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Straightforward synthesis of functionalized chroman-4-ones through cascade radical cyclization-coupling of 2-(allyloxy)arylaldehydes†

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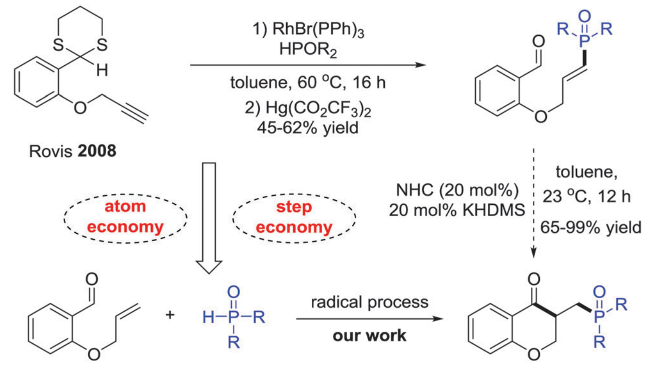
A novel and direct approach to synthesize a series of phosphonate, azide and hydroxy functionalized chroman-4-ones has been developed. The cascade transformation appears to proceed through an intramolecular addition of an *in situ* generated acyl radical onto the alkene, followed by a selective nucleophilic radical–electrophilic radical cross coupling.

The chroman-4-one scaffold with functional groups widely exists in natural products, and has found abundant applications in biological and medicinal compounds.[1] Consequently, the development of atom-economical and efficient approaches to synthesize these functionalized chroman-4-ones has attracted much attention.[2] The internal hydroacylation between an aldehyde and alkene provides an elegant route to produce the chroman-4-one skeleton.[3] Beyond that, sequentially coupling hydroacylation[4] with another functionalization[5] of unactivated alkenes may represent one of the most direct routes to functionalized chroman-4-ones.

As a representative example, phosphonate chroman-4-ones could be synthesized *via* a polarity reversal strategy enabled by the N-heterocyclic carbene (NHC) catalyzed Stetter reaction of (vinylphosphonate)arylaldehyde, which was obtained by the Rh-catalyzed hydrophosphinylation of a protected functional alkyne (Scheme 1).[6] Inverse synthetic analysis indicated that these compounds could possibly be prepared through a more straightforward hydroacylation–phosphorylation of 2-(allyloxy)arylaldehydes, and it could be assumed to proceed in the following way: the *in situ* generated acyl radical species would react with the neighbouring alkene (similar to the hydroacylation reaction in form) to generate an active cyclic alkyl radical intermediate, which could undergo a second functionalization by cross coupling with another functional radical, such as a phosphonyl-, azide-, or hydroxyl-radical.



Scheme 1 N-heterocyclic carbene and radical approaches to 3-(phosphonomethyl)chroman-4-ones.

In 2012, we reported the first Pd-catalyzed C–P bond formation *via* direct oxidative coupling between the Csp^2–H of azole and the P–H of dialkyl phosphite. This transformation was determined to be a non-radical process.[7] It has been demonstrated that silver salts/$K_2S_2O_8$ are efficient catalyst systems for phosphonyl radicals initiating.[8] Therefore, we started our conditions screening from a model reaction of 2-(allyloxy)benzaldehyde **1a** and diethyl phosphite **2a**, and the desired product **3aa** was obtained in 16% yield using $AgNO_3$ as the metal catalyst and $K_2S_2O_8$ as the oxidant in DMSO at room temperature (Table 1, entry 1). The yield of **3aa** rose up to 48% when running the reaction at a slightly higher temperature (35 °C) (Table 1, entry 2). Further raising the temperature instead decreased the reactivity (Table 1, entry 3). When replacing the oxidant $K_2S_2O_8$ with $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, $Mg(NO_3)_2{\cdot}6H_2O$ or $Cu(NO_3)_2{\cdot}6H_2O$, lower or even no yields were obtained (Table 1, entries 4–7). Compared with DMSO, a wide range of other solvents, such as toluene, dioxane, MeCN, THF, DCE, DCM, DMF, EtOAc, and MeOH, all gave much lower **3aa** yields (see Table S1 in the ESI†). Because of the important role of $K_2S_2O_8$ in generating the

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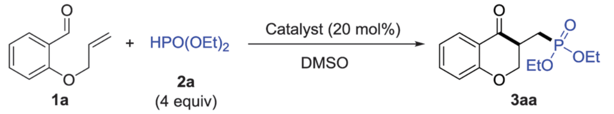
Table 1 Optimization of the reaction conditions[a]

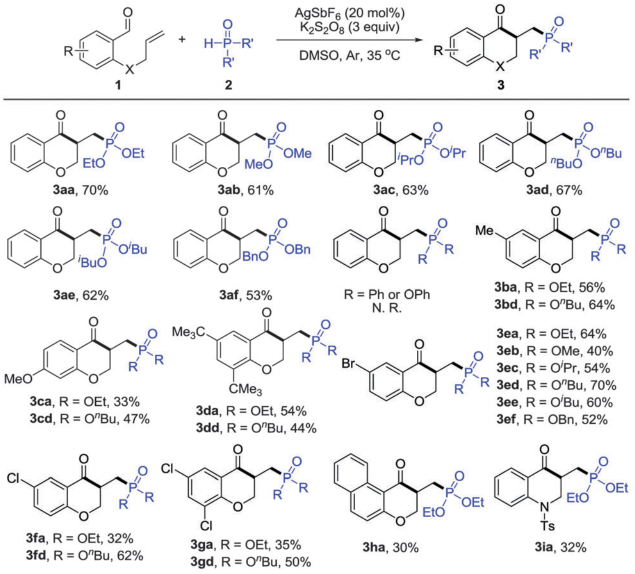


Entry	Catalyst	Oxidant (equiv.)	Temp. (°C)	Yield (%)
1	$AgNO_3$	$K_2S_2O_8$ (4)	25	16
2	$AgNO_3$	$K_2S_2O_8$ (4)	35	48
3	$AgNO_3$	$K_2S_2O_8$ (4)	50	36
4	$AgNO_3$	$Na_2S_2O_8$ (4)	35	30
5	$AgNO_3$	$(NH_4)_2S_2O_8$ (4)	35	27
6	$AgNO_3$	$Mg(NO_3)_2 \cdot 6H_2O$ (2)	35	0
7	$AgNO_3$	$Cu(NO_3)_2 \cdot 6H_2O$ (2)	35	0
8	$AgNO_3$	$K_2S_2O_8$ (3)	35	50
9	$AgNO_3$	$K_2S_2O_8$ (2)	35	33
10[b]	$AgNO_3$	$K_2S_2O_8$ (3)	35	35
11[c]	$AgNO_3$	$K_2S_2O_8$ (3)	35	45
12	AgOTf	$K_2S_2O_8$ (3)	35	51
13	Ag_2CO_3	$K_2S_2O_8$ (3)	35	49
14	Ag_2SO_4	$K_2S_2O_8$ (3)	35	58
15	Ag_2SO_3	$K_2S_2O_8$ (3)	35	49
16	Ag_2O	$K_2S_2O_8$ (3)	35	45
17	AgOAc	$K_2S_2O_8$ (3)	35	49
18	$AgSbF_6$	$K_2S_2O_8$ (3)	35	63
19[d]	**$AgSbF_6$**	**$K_2S_2O_8$ (3)**	**35**	**70**
20[d,e]	$AgSbF_6$	$K_2S_2O_8$ (3)	35	47
21		$K_2S_2O_8$ (3)	35	Trace
22[f]	$AgSbF_6$		35	0

[a] All reactions were carried out on a 0.3 mmol scale in DMSO (3 mL) for 5 h. Reported yields are the isolated yields. [b] 3 equiv. of diethyl phosphite. [c] 5 equiv. of diethyl phosphite. [d] Under Ar. [e] 10 mol% of $AgSbF_6$ for 12 h. [f] 200 mol% of $AgSbF_6$.

phosphonyl radical, the ratio of **2a** and $K_2S_2O_8$ significantly affects the reactivity, and a 50% yield of **3aa** was realized using 4 equiv. of **2a** and 3 equiv. of $K_2S_2O_8$ (Table 1, entries 8–11). Upon using various silver salts as the catalyst, $AgSbF_6$ displayed the best catalytic activity, giving the desired **3aa** in 63% yield (Table 1, entries 12–18), and the yield of **3aa** could be improved to 70% under an argon atmosphere (Table 1, entry 19). However, only 47% yield of **3aa** was obtained when reducing the amount of silver catalyst (Table 1, entry 20). It is worth noting that both the silver catalyst and oxidant are indispensable in this transformation (Table 1, entries 21 and 22).

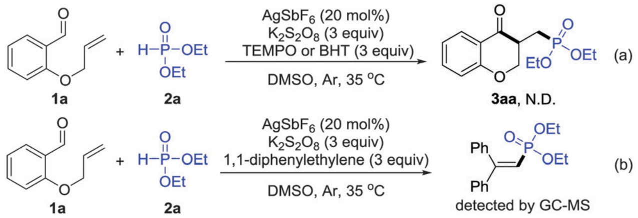
With the optimized conditions in hand (Table 1, entry 19), we then turned our attention to examining the scope and limitations of this method (Scheme 2). First, we evaluated a series of phosphonyl compounds. Dialkyl phosphites afforded the corresponding products in moderate to good yields (**3aa–3af**). Unfortunately, diphenylphosphine oxide and diphenyl arylaldehydesnate were not suitable for this transformation. Subsequently, a series of 2-(allyloxy)arylaldehydes were investigated. The benzene rings with electron-donating (Me, OMe and *tert*-butyl) and -withdrawing (Br and Cl) groups all worked smoothly with dialkyl phosphites, affording the desired phosphonate chroman-4-ones in 32% to 70% yields (**3ba–3ga**, **3bd–3gd**). 2-(Allyloxy)-1-naphthaldehyde also worked using this transformation, affording **3ha** in 30% yield. Furthermore, phosphonate 2,3-dihydroquinolin-4-one **3ia** with a nitrogen atom in the skeleton could also be synthesized by this procedure.



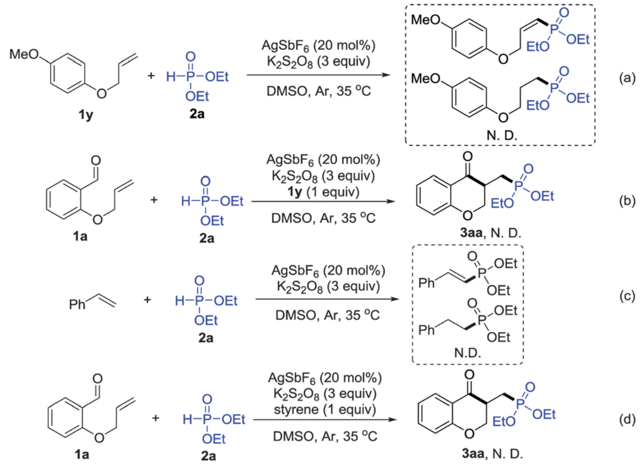
Scheme 2 Scope of the phosphonyl compounds and 2-(allyloxy)arylaldehydes. Reaction conditions: **1** (0.3 mmol), **2** (1.2 mmol), $AgSbF_6$ (0.06 mmol) and $K_2S_2O_8$ (0.9 mmol) in DMSO (3 mL) at 35 °C for 5 h under Ar. Reported yields are isolated yields.

To study the proposed mechanism, a series of radical trapping experiments was carried out. The common radical scavengers TEMPO (2,2,6,6-tetramethylpiperidinooxy) and BHT (butylated hydroxytoluene) could prevent the reaction completely (Scheme 3a). This reaction could also be suppressed by 1,1-diphenylethylene. Besides, a little of the coupling product of the phosphonyl radical with 1,1-diphenylethylene was detected by GC-MS (Scheme 3b). These results not only suggest that the reaction experiences a radical process, but also indicate that a phosphonyl radical could be involved in this transformation.

Such a transformation involving C–C and C–P bond formations is proposed to proceed *via* either an acyl radical addition to the alkene or a phosphate radical addition to the alkene.[9,10] To gain more insights into the reaction pathway, the following control experiments were conducted. The reaction of 1-(allyloxy)-4-methoxybenzene **1y** and **2a** did not afford the desired phosphate derivatives and 90% of **1y** was recovered (Scheme 4a). Surprisingly, the product **3aa** was not detected when **1y** was added to the model reaction, 88% of **1a** and 92% of **1y** were recovered (Scheme 4b). These two results appear to indicate that the addition of a phosphonyl radical onto the alkene was not involved in the transformation, although the presence of a phosphonyl radical was indicated by the reaction



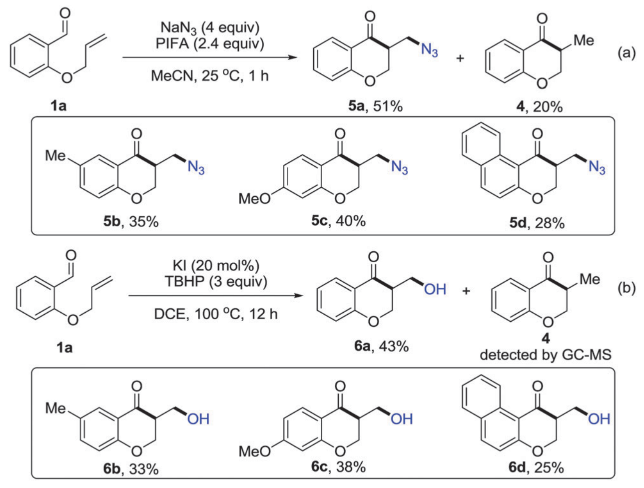
Scheme 3 Radical trapping experiments.



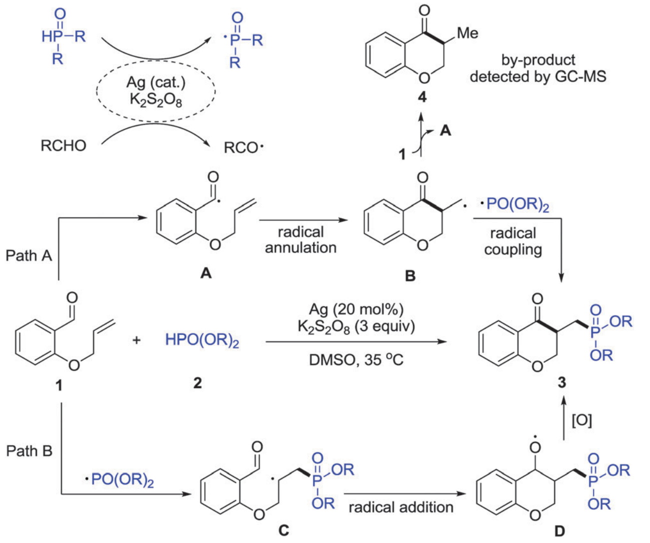
Scheme 4 Control experiments.

in Scheme 3b. In addition, **1y** could prevent the reaction from occurring. The addition products of the phosphonyl radical and styrene were also not observed, and the styrene was found to be polymerized (Scheme 4c). Similar to **1y**, styrene could also inhibit the reaction (Scheme 4d). These results further excluded the possibility that the reaction underwent a phosphonyl radical addition to the alkene. Based on the above investigations, it could be tentatively assumed that this cascade reaction preferred to undergo an acyl radical addition onto the alkene.

In order to further verify and extend the application of the above strategy involving acyl radical cascade cyclization with an alkene and subsequent coupling with another electrophilic radical, we tested the reaction of **1a** with other radicals. It has been reported that the azide radical[11] or peroxide[12] could initiate aldehydes to generate acyl radicals. To our delight, **1a** could transform into the desired N_3 functionalized chroman-4-one **5a** in 51% yield under an azide radical generating reaction system, and by-product **4** was obtained in 20% yield (Scheme 5a). Other azide chroman-4-one derivatives (Me, OMe and naphthalene) were obtained in 28% to 40% yields (**5b–5d**). In addition, the desired hydroxyl chroman-4-one **6a** was isolated from the reaction of **1a** with a hydroxyl radical produced by KI/TBHP in 43% yield, and **4** was also detected by GC-MS (Scheme 5b). Similarly, other hydroxyl chroman-4-one derivatives (Me, OMe and naphthalene) were synthesized in 25% to 38% yields *via* the same strategy (**6b–6d**). These results further indicate that these reactions underwent an intramolecular addition of the acyl radical to the alkene, followed by a selective coupling between the nucleophilic alkyl radical and electrophilic azide radical[13] or hydroxyl radical.[14]



Scheme 5 Synthesis of 3-(azidomethyl) and 3-(hydroxymethyl) chroman-4-ones.



Scheme 6 Plausible reaction mechanisms.

Based on the above experiments, a proposed mechanism is drawn in Scheme 6. Initially, acyl radical **A**[15] and a phosphonyl radical were initiated from **1** and **2** under the catalysis of a silver catalyst and $K_2S_2O_8$. Then **A** undergoes an intramolecular cyclization to generate a new alkyl radical **B.**[10] Finally, the desired product **3** is obtained *via* the coupling of nucleophilic alkyl radical **B** and an electrophilic phosphonyl radical (Scheme 6, Path A).[16] Inevitably, radical **B** might transform into the by-product **4** *via* hydrogen abstraction from **1** along with the regeneration of **A**. Alternatively, the formation of **3** could possibly be due to the addition of a phosphorus radical to the alkene,[9] followed by the addition of alkyl radical **C** to the C═O bond generating oxygen radical **D**. Eventually, **D** could convert to **3** *via* a single electron oxidation process (Scheme 6, Path B).[17] Based on the control experiments (Scheme 4) and the formation of by-product **4**, we are inclined to favour the formation of **3** *via* Path A. Likewise, the formation of the azido and hydroxyl chroman-4-ones may follow Path A.

In summary, we have developed a novel and straightforward approach to synthesize phosphonate chroman-4-ones. The reaction employs a simple silver salt as the catalyst and $K_2S_2O_8$ as an oxidant under mild conditions. It was found to involve an alkyl radical intermediate **B** generated by acyl radical addition to the alkene, followed by its selectively coupling with a phosphonyl radical. Interestingly, such an acyl radical addition onto a neighbouring alkene and a subsequent radical/radical cross coupling strategy could also extend to azido and hydroxyl radicals, and the synthesis of the corresponding functionalized chroman-4-ones was achieved smoothly. The successful application of the present strategy for the diverse and green synthesis of functional compounds will stimulate more interest on the development of radical-involving cascade reactions.

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