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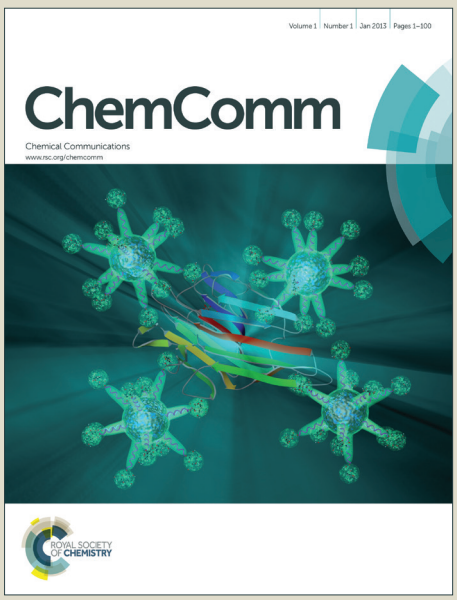

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$Pd(OAc)_2/S{=}PPh_3$ Accelerated Activation of *gem*-Dichloroalkenes for the Construction of 3-Arylchromones

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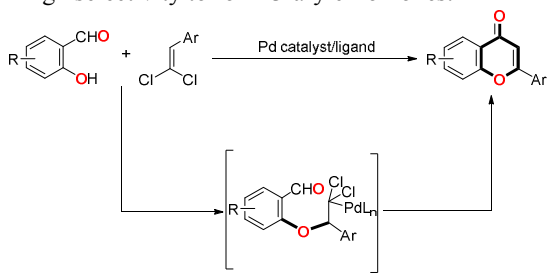
The Pd-catalyzed regioselectively intramolecular nucleophilic substitution of *gem*-dichloroalkenes derivatives with salicylaldehydes leading to synthesis of 3-arylchromones has been developed. $Pd(OAc)_2/S{=}PPh_3$ could activate the *gem*-dichloroalkenes and undergo the nucleophilic substitution by salicylaldehydes with the aid of base.

gem-Dichloroalkenes have been emerged as a powerful and versatile building block to construct the various heterocycles and carbocycles,[1] owing to high regioselectivity and easy accessibility from simple materials. Up to now, the tandem intramolecular C-N process of *gem*-dichloroalkenes has been employed to the formation of indoles and thienopyrroles by palladium catalysts.[2] However, the tandem intramolecular nucleophilic substitutions of *gem*-dichloroalkenes to construct the heterocycles are relatively less demonstrated owing to seeking the appropriate reagent to activate the *gem*-dichloroalkenes. Herein, the cascade reaction of *gem*-dichloroalkenes to produce the six-membered-ring oxygen heterocycles is an almost untouched area. Therefore, further research in this area is still challenged.

Flavones are an intriguing group of six-membered-ring oxygen heterocycles and have been examined to possess remarkable anti-inflammatory, antioxidant and anti-carcinogenic properties,[3, 4] which have led to the continual discovery and synthesis of flavones. Recently, 3-arylchromones have been of particular interest, owing to some privileged molecules and their unique biological activities.[5] Over the last two decades, construction of flavones has been mainly based on the follow strategies: cyclization of l-(2-X-phenyl)-3-phenyl-1,3-propanediones (X = OH, OR, Br, Cl) or 2'-hydroxychalcones,[6,7] Pd-catalyzed oxidative arylation of chromones with phenylboronic acids,[8] Pd-catalyzed carbonylative cyclization using CO gas as carbonyl resource.[9] In spite of the impressive progress made in the preparation of flavones and their derivatives,[10] more general and substrate easily available routes would be still highly desirable. Salicylaldehydes and *gem*-dichloroalkenes were widely existed in the organic reagents as the available starting materials. We envisioned that $Pd(OAc)_2$/ triphenylphosphine sulfide ($S{=}PPh_3$) could promote the activation of *gem*-dichloroalkenes to undergo the followed nucleophilic substitution. After the direct β-hydride elimination and hydride re-insertion, *gem*-dichloroalkenes would be significant to construct the C-O bond and C=O bond to form the desired chromones (Scheme 1). In this communication, with $Pd(OAc)_2/S{=}PPh_3$ as the catalyst, *gem*-dichloroalkenes and salicylaldehydes could be performed well in high selectivity to form 3-arylchromones.

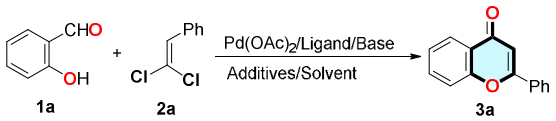


Scheme 1. Synthesis of 3-arylchromones from salicylaldehydes and *gem*-dichloroalkenes

We began our investigation with the reaction of salicylaldehyde **1a** in the presence of $Pd(OAc)_2/S{=}PPh_3$, K_2HPO_4 and benzyltriethylammonium chloride (TEBAC) under N_2 atmosphere at 110 °C in NMP for 24 h. Gratifyingly,

the desired 3-phenylchromones **3a** was obtained in 54% yield (Table 1, entry 1). After examining several bases, Na_2CO_3 was found to be the most efficient for this reaction (Table 1, entries 2-4). Based on initial speculation that the solvents would affect the reaction selectivity, a series of solvents were examined (Table 1, entries 4-8). Use of DMSO and toluene led to no reaction or only a trace amount of the desired product. Interestingly, with diglyme, NMP and DMF, the reaction showed excellent activity to afford the desired product in good yields. During optimization studies, TEBAC and TBAF were applied to the tandem reaction with both of them displaying the same levels of positive effect on the product yield (Table 1, entries 4 and 10). While TBAB was carried out, no positive result was obtained (Table 1, entry 9). Then we examined the effect of the ligand, the results indicated that $S=PPh_3$ and $O=PPh_3$ were effectively promoted in the activation of *gem*-dichloroalkenes (Table 1, entries 10 and 12). In above process, $S=PPh_3$ was not a strong σ -donor for Pd(II), the formation of intermediate and subsequent catalytic reactions on Pd(II) were not likely to be blocked.[11] Meanwhile, the desired product was not obtained under the condition without ligands, additives and Pd catalyst added (Table 1, entries 11, 13, 14, and 15). Notably, no desired product was observed in the presence of air because (2, 2-dichlorovinyl)benzene was converted completely into 1, 4-diphenylbuta-1, 3-diyne (Table 1, entry 16).

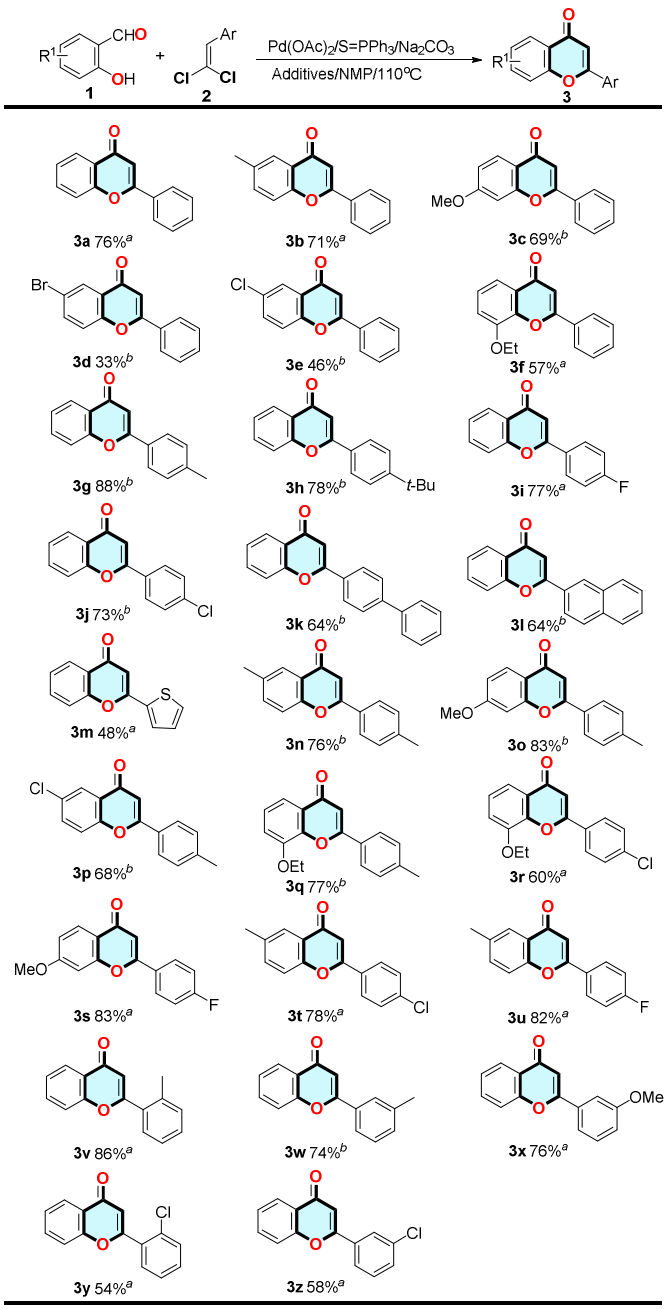
Table 1 Optimization of the reaction conditions.[a]



Entry	Additives	Ligand	Base	Solvent	Yield (%)[b]
1	TEBAC	$S=PPh_3$	K_2HPO_4	NMP	54
2	TEBAC	$S=PPh_3$	K_2CO_3	NMP	26
3	TEBAC	$S=PPh_3$	NaOAc	NMP	20
4	**TEBAC**	**$S=PPh_3$**	**Na_2CO_3**	**NMP**	**76**
5	TEBAC	$S=PPh_3$	Na_2CO_3	DMSO	trace
6	TEBAC	$S=PPh_3$	Na_2CO_3	DMF	70
7	TEBAC	$S=PPh_3$	Na_2CO_3	Diglyme	69
8	TEBAC	$S=PPh_3$	Na_2CO_3	Toluene	trace
9	TBAB	$S=PPh_3$	Na_2CO_3	NMP	trace
10	TBAF	$S=PPh_3$	Na_2CO_3	NMP	74
11	--	$S=PPh_3$	Na_2CO_3	NMP	N.D.
12	TEBAC	$O=PPh_3$	Na_2CO_3	NMP	67
13	TEBAC	--	Na_2CO_3	NMP	N.D.
14	TEBAC	PPh_3	Na_2CO_3	NMP	trace
15[c]	TEBAC	$S=PPh_3$	Na_2CO_3	NMP	N. D.
16[d]	TEBAC	$S=PPh_3$	Na_2CO_3	NMP	N. D.

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), additives (1.0 mmol), base (1.5 mmol), solvent (2.0 mL), 110 °C, N_2, 24 h. [b]Isolated yield. [c]$Pd(OAc)_2$ was not added. [d]In air.

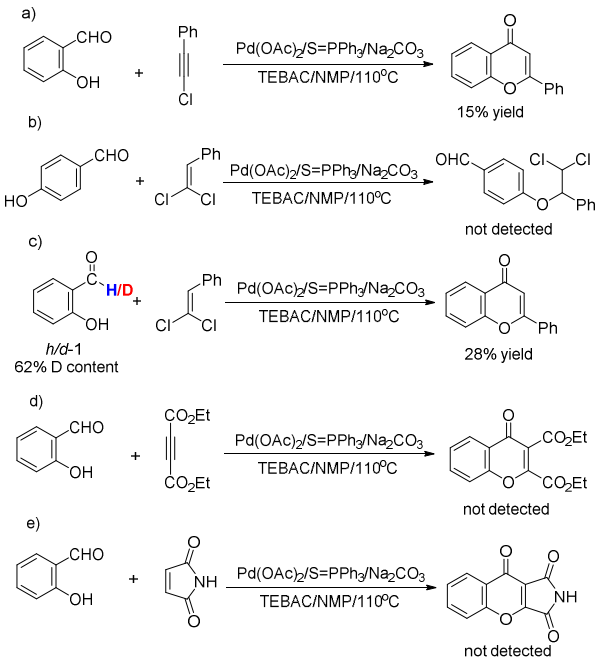
To gain insight into the tolerance of this reaction, we had investigated the reaction scope with various salicylaldehydes and (2, 2-dichlorovinyl)benzene under the optimized conditions (Scheme 2). The coupling reaction of salicylaldehydes bearing electron-withdrawing groups and electron-donating groups proceeded smoothly to provide the corresponding 3-arylchromones in good to excellent yields (Scheme 2, **3a**-**3f**).



Scheme 2. Scope of the cyclization of salicylaldehydes and *gem*-dichloroalkenes. [a]Reaction conditions: **1** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), $S=PPh_3$ (10 mol%), TEBAC (1.0 mmol), Na_2CO_3 (1.5 mmol), NMP (2.0 mL), 110 °C, N_2, 24 h, isolated yield. [b]TBAF (1.0 mmol) was used.

These results indicated that the present reaction showed good functional-group tolerance of salicylaldehydes. Furthermore, various *gem*-dichloroalkenes on the phenyl ring (methyl, tertiary butyl, chloro, fluoro, phenyl and naphthyl substituents) underwent the cyclization to generate the desired product from 64% to 88% yield (Scheme 2, **3g**-**3l**). To our delight, thiophene substituted gem-dichloroalkenes was similarly found to be the suitable substrate for this transformation and afforded the desired

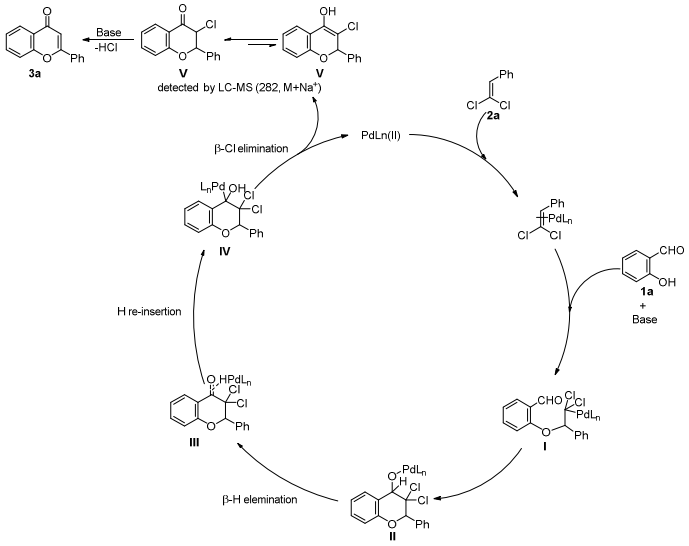
product in moderate yield (Scheme 2, **3m**). Inspired by these results, salicylaldehydes with methyl, methoxyl, ethoxyl, and chlorine substituents were well coupled with substituents *gem*-dichloroalkenes to provide the corresponding chromones in good to excellent yields (Scheme 2, **3n-3u**). It was found that there was no significant difference in reactivity between different substituents *gem*-dichloroalkenes and salicylaldehydes. Finally, the aromatic *ortho* and *meta*-substitution of dichlorostyrenes were explored to afford the desired product in 54%-86% yield (Scheme 2, **3v-3z**). In all, this reaction provided a practical application for the construction of 3-arylchromones by the easily available starting materials.



Scheme 3. Preliminary mechanistic study.

Some control experiments were conducted to gain some insight into the reaction mechanism. Firstly, the reaction of salicylaldehyde with (chloroethynyl)benzene produced 2-phenyl-4H-chromen-4-one in 15% yield (Scheme **3a**). This result indicated that (2, 2-dichlorovinyl)benzene would not fully convert to (chloroethynyl)benzene to participate the cascade reaction. Furthermore, when 4-hydroxybenzaldehyde reacted with **1a**, no desired product was obtained and most of *gem*-dichloroalkene was transformed to the 1, 4-diphenylbuta-1, 3-diyne. It was clearly shown that the aldehyde group was not only coupled with *gem*-dichloroalkene, but also possessed the directing role (Scheme **3b**). When 62% D content of salicylaldehyde was applied to couple with (2, 2-dichlorovinyl)benzene, non-deuterium distribution was observed in the final product (Scheme **3c**). It was demonstrated that the hydrogen atom from the aldehyde and hydroxy of salicylaldehyde was eliminated in the reaction. Finally, the exposure of diethyl but-2-ynedioate and 1*H*-pyrrole-2, 5-dione to the standard reaction conditions failed to deliver any positive result, thus suggesting that the process of Diels-Alder could not be involved in the reaction (Scheme **3d** and **3e**).

A proposed mechanism for the $Pd(OAc)_2/S=PPh_3$ catalyzed annulation of *gem*-dichloroalkene with salicylaldehyde is described in Scheme 4. Based on previous reports and experiences,[12] *gem*-dichloroalkene activated by $Pd(OAc)_2/S=PPh_3$ underwent nucleophilic addition of salicylaldehyde to generate intermediate **I**. Subsequently, intermediate **II** was obtained by the insertion of the aldehyde group. The direct β-hydride elimination occured at intermediate **II** to afford intermediate **III**. The hydride re-insertion of intermediate **III** released intermediate **IV**. Intermediate **V** obtained from the β-chloride elimination of intermediate **IV**. Finally, the chloride elimination of intermediate **V** produced the desired product **3a**.



Scheme 4. Proposed catalytic cycles for the construction of chromone.

In conclusion, we have developed an efficient route to construct the 3-arylchromones by palladium catalyzed cascade reaction between salicylaldehydes and *gem*-dichloroalkenes. In this process, $Pd(OAc)_2/S=PPh_3$ plays a decisive role to accelerate the activation of *gem*-dichloroalkene to couple well with salicylaldehydes. This approach enables the application of a cascade reaction to synthesis the highly functionalized chromones from available starting materials. It would be believed that these results may inspire much future effort towards the development of $Pd(OAc)_2/S=PPh_3$ activated dichloroalkenes to construct the heterocycle compounds.

Acknowledgements

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Notes and references

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