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Palladium catalyzed Heck-arylation/cyclization cascade: An environmentally benign and efficient synthesis of 4-arylcoumarins in water

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ABSTRACT

An environmentally benign and efficient approach for the synthesis of 4-arylcoumarins from *ortho*-hydroxy cinnamate ester derivatives with aryl iodides was developed in water under aerobic conditions. This transformation proceeds through a palladium catalyzed Heck-arylation/cyclization cascade reaction. The present protocol features a wide substrate scope and readily available starting materials to afford the desired products in high to excellent yields.

Introduction

Coumarins are useful natural products widely found in plants and exhibit a broad range of biological and pharmacological activity.[1] In addition, coumarins are aslo used as synthetic building blocks in the pharmaceutical, perfume, and agrochemical industries, as well as additives in food and cosmetics.[2] In coumarin derivatives, 4-aryl derivatives constitute a subgroup of favonoids that have received considerable attention, as they display excellent biological activities including antitumor,[3a] anti-HIV,[3b,3c] anticoagulation, antibacterial,[3d] antiinflammatory,[3e,3f] and antioxidant.[3g]

Traditionally, 4-arylcoumarins have been obtained from phenols by means of condensation reactions with carbonyl compounds such as Pechmann or Perkin reactions,[4] These methods usually occur under harsh conditions, and low regioselectivities are typically observed, which may lead to difficulty for further derivatization and product separation. In this respect, transition-metal-catalyzed Suzuki or Stille coupling reactions of coumarin scaffolds with a coupling point at the 4 position for 4-arylcoumarins have been developed.[5–8] However, these starting materials (halides, pseudohalides and organometallic reagents) for such processes need to be prefunctionalized, making these reactions unfavorable environmentally. Other transition-metal-catalyzed protocols, such as palladium-catalyzed tandem Heck-lactonization from o-iodophenols and enoates,[9] palladium-catalyzed oxidative annulation of phenols with propargylic esters or acrylates,[10] and palladium-catalyzed direct oxidative cyclocarbonylation of 2-vinylphenols[11] for the synthesis of 4-arylcoumarins were reported as well. Recently, Duan and coworkers reported an efficient protocol for the direct synthesis of 4-arylcoumarins *via* palladium-catalyzed oxidative Heck coupling reaction of coumarins and arylboronic acids.[12] Another simple and efficient procedure for the synthesis of 4-arylcoumarins one that is less investigated, is the palladium catalyzed Heck-arylation/cyclization of o-hydroxycinnamates with various electrophilic coupling partners. Initially, this approach was reported in 2005 by using aryl halides in a molten ^{n}-Bu_4NOAc/^{n}-Bu_4NBr mixture (Scheme 1a).[13a] Later on, the approach was modified by the use of aryl diazonium salts in methanol (Scheme 1b).[13b] Finally, diaryliodonium(III) salts were successfully used to perform this transformation by using dimethylformamide[13c] and ethanol[13d] as solvents, respectively (Scheme 1c and d). In all cases, the present Heck-arylation/cyclization protocol is an elegant method for synthesis of 4-arylcoumarins derivatives. However, the aryl halide partner such as electron-poor aryl bromides and aryl iodides only offer moderate yields; moreover, the other two aryl salts partners are not commercially and always unstable. Therefore, the exploration

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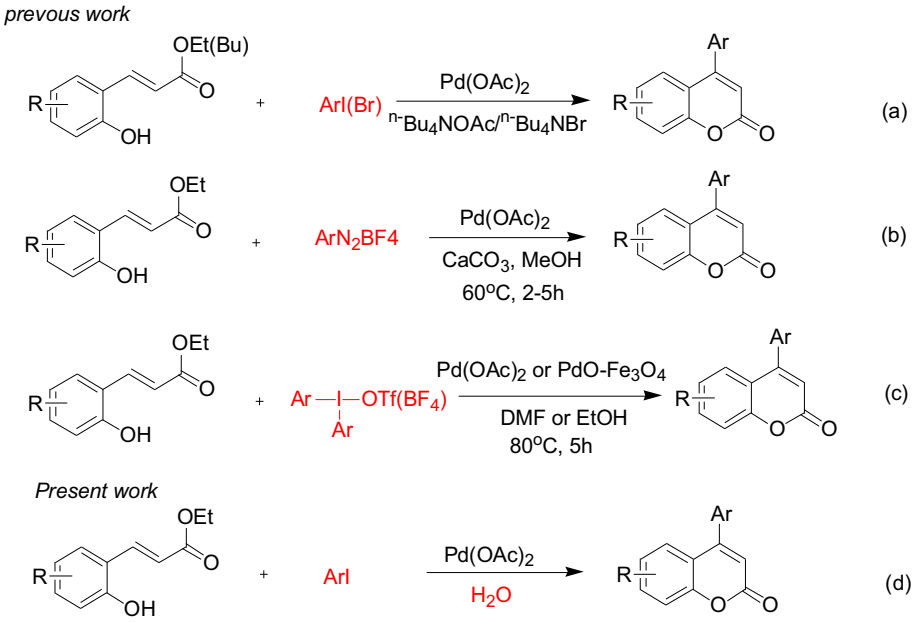


Scheme 1. Palladium catalyzed Heck-arylation/cyclization of *ortho*-hydroxy cinnamate with various electrophilic coupling partners.

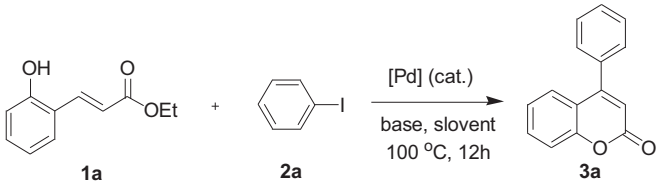
of an atom-economic and environmentally friendly method for the construction of 4-arylcoumarins remains a challenging task, and therefore merits further consideration. Herein, we would like to disclose our realization of the synthesis of 4-arylcoumarins by palladium-catalyzed Heck-arylation/cyclization of *ortho*-hydroxy cinnamates with aryl iodides in water.

Results and discussion

We began our study by examining the reaction of ethyl *ortho*-hydroxy cinnamate **1a** and phenyl iodide **2a** as the model substrates to optimize the formation of 4-arylcoumarin **3a** under various conditions. Unexpectedly, the desired product of **3a** was obtained in 23% yield in the presence of 10 mol% $Pd(OAc)_2$ as catalyst and 2 equiv NaOAc as base in xylene at 100 °C for 12 h (Table 1, entry 1). Initially, we screened various solvents, it was found that the yield of **3a** was slightly improved in dioxane or MeCN (Table 1, entries 2,3). Moderate yields were obtained in DMF or DMSO (Table 1, entries 4,5). To our delight, the desired product **3a** was obtained in 89% and 91% yields by using PEG-400 and EtOH as solvents, respectively (Table 1, entry 6,7). However, only moderate yields were obtained by using *t*-Amy-OH and AcOH as solvents (Table 1, entries 8,9). Interestingly, we found that the similar yield was obtained in H_2O as a sole solvent (Table 1, entries 7 *vs* 10). Then, screening of other bases was attempted, the desired product **3a** was obtained in high yields by employing K_3PO_4 and $NaHCO_3$ as bases (Table 1, entries 11,12). The other bases such as Na_2CO_3, Cs_2CO_3, K_2CO_3 and NaOH were less effective to promote the transformation (Table 1, entries 13–16). Finally, the palladium catalysts were investigated. Inferior results were given by Pd(C) and $Pd_2(dba)_3$ (Table 1, entries 17,18). The other palladium salts such as $Pd(PPh_3)_4$, $PdCl_2$, $PdCl_2(PPh_3)_2$ and $Pd(OOCCF_3)_2$ can also promote the transformation in very high yields when the reaction was carried out in similar condition reactions (Table 1, entries 19–22). Finally, we found that $PdCl_2(CH_3CN)_2$ was the best choice and the desired product **3a** was obtained in 95% yield (Table 1, entry 23). In addition, lowering the reaction temperature caused the yield drastically descend (Table 1, entry 24). Attempts to lower the catalyst loading from 10 to 5 mol% resulted in decreased yield (73%, Table 1, entry 25). Control experiments have, however, proven that, in the absence of catalyst or base, no reaction took place (Table 1, entries 26,27). Overall, the catalytic protocol using $PdCl_2(CH_3CN)_2$ as catalyst with NaOAc as base in H_2O at 100 °C was found to be the most effective combination for obtaining an excellent yield (Table 1, entry 23).

Under the optimized reaction conditions (Table 1, entry 23), we decided to test a wide range of aryl iodides **2** to evaluate the scope of the arylation/cyclization protocol. As shown in Table 2, aryl iodides possessing electron-neutral, electrondonating or electron-withdrawing groups were well tolerated and smoothly underwent arylation/cyclization reactions to result in variously functionalized 4-arylcoumarins in good to excellent yields. Furthermore, the substitution patterns had no influence on the present transformation reactions. For example, aryl iodides having a methyl group at the *para*, *meta*, or *ortho* position, respectively, afforded the desired 4-aryl coumarins **3b–d** in excellent yields. Aryl iodide bearing two methyl groups at *meta* positions was tolerated and gave the corresponding coupling products **3e** in 92%yields. Similarly, methoxy group at the *para*, *meta*, or *ortho* position also provided the corresponding arylation/cyclization products **3f–h** in excellent yields. Specifically, halogen substituents such as fluoro, chloro and bromo were well tolerated, and gave the corresponding products **3i–n** in high to excellent yields. These functional groups are useful synthetic handles for further derivatizations. Additionally, aryl iodides bearing an electron-withdrawing group were well-tolerated under the optimized reaction conditions. For example, aryl iodides bearing strong EWG such as trifluoromethyl, acetyl, and carboxylic acid methyl ester afforded the desired products **3o–q** in high yields. It is interesting to mention that aryl iodide bearing a free amino group at *para* position was well tolerated, and gave the corresponding products **3r** in 67% yield. The 1-iodo-naphthalene was a good substrate and gave the desired product **3s** in 77% yield. The reaction also proceeded well with heterocyclic coupling partners; for example, 3-iodopyridine and 3-iodothiophene gave the desired products **3*t*–u** in good yields. In order to further explore the generality of this procedure, we turned our attention to further expand the scope of the reaction to other *ortho*-hydroxycinnamate **1**. For example, the *ortho*-hydroxycinnamates **1b–f** bearing methyl, bromo, and chloro substituents were used and afforded the

Table 1
Optimization of the Reaction Conditions.



Entry[a]	Catalyst	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	NaOAc	Xylene	23
2	$Pd(OAc)_2$	NaOAc	Dioxane	26
3	$Pd(OAc)_2$	NaOAc	MeCN	32
4	$Pd(OAc)_2$	NaOAc	DMF	46
5	$Pd(OAc)_2$	NaOAc	DMSO	42
6	$Pd(OAc)_2$	NaOAc	PEG-400	89
7	$Pd(OAc)_2$	NaOAc	EtOH	91
8	$Pd(OAc)_2$	NaOAc	*t*-Amy-OH	36
9	$Pd(OAc)_2$	NaOAc	AcOH	40
10	$Pd(OAc)_2$	NaOAc	H_2O	87
11	$Pd(OAc)_2$	K_3PO_4	H_2O	78
12	$Pd(OAc)_2$	$NaHCO_3$	H_2O	83
13	$Pd(OAc)_2$	Na_2CO_3	H_2O	33
14	$Pd(OAc)_2$	Cs_2CO_3	H_2O	28
15	$Pd(OAc)_2$	K_2CO_3	H_2O	26
16	$Pd(OAc)_2$	NaOH	H_2O	24
17	Pd(C)	NaOAc	H_2O	41
18	$Pd_2(dba)_3$	NaOAc	H_2O	32
19	$Pd(PPh_3)_4$	NaOAc	H_2O	82
20	$PdCl_2$	NaOAc	H_2O	92
21	$PdCl_2(PPh_3)_2$	NaOAc	H_2O	86
22	$Pd(OOCCF_3)_2$	NaOAc	H_2O	88
23	$PdCl_2(CH_3CN)_2$	NaOAc	H_2O	95
24[c]	$PdCl_2(CH_3CN)_2$	NaOAc	H_2O	46
25[d]	$PdCl_2(CH_3CN)_2$	NaOAc	H_2O	73
26	$PdCl_2(CH_3CN)_2$	–	H_2O	NR
27	–	NaOAc	H_2O	NR

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), Pd catalyst (10 mol%), base (1.0 mmol), solvent (1 mL), 100 °C, 12 h, NR: no reaction.
[b] Isolated yield.
[c] Reaction at 50 °C.
[d] 5 mol% $PdCl_2(CH_3CN)_2$ was used.

corresponding products **3v–z** in excellent yields. However, some limitations were observed, aryl iodides bearing strong EWG such as p-CN or p-NO_2 were ineffective and only trace amount of the corresponding products **3aa–ab** were detected. Moreover, *ortho*-hydroxycinnamates **1** bearing a methoxyl group at 5-positon failed to provide the corresponding 4-aryl coumarins **3ac** under the present optimized reaction conditions.

Some preliminary mechanistic studies were carried out to probe whether the reaction takes place through a cyclization/Heck-arylation or through a Heck-arylation and then a subsequent cyclization (Scheme 2). Firstly, 2H-chromen-2-one **4** was treated with phenyl iodide **2a** under standard conditions, only the starting substrates were recovered (Scheme 2a). These results suggest that the first pathway is unlikely. Secondly, to investigate whether the Heck-arylation reaction took place first, followed by cyclization, the substrate **5** without OH group was tested and the desired Heck-arylation product **6** was afforded in 91% yield under the under standard conditions (Scheme 2b). To Furthermore further probe whether the arylation reaction takes place through the normal Heck-arylation reaction or through OH group directed C—H activation/arylation reaction, an intermolecular competitive reaction with equimolar amount of **1a** and **5** was conducted under the standard conditions and the corresponding products (the mol ratio of **3a**:**6** is 53:47) were obtained (Scheme 2c). It suggests that the first arylation reaction occurred through the classical Heck-arylation reaction.

Based on our experimental results, this pathway is analogous in a number of respects to that proposed by Ramón for palladium catalyzed cascade Heck-arylation/cyclization reaction of *ortho*-hydroxy cinnamate ester with diaryliodonium salts.[13d] Therefore, a possible reaction pathway for the formation of 4-arylcoumarins is outlined in Scheme 3.

In conclusion, we have developed an efficient, environmentally benign method for the synthesis of 4-aryl coumarins. This transformation preceded *via* a palladium catalyzed tandem Heck-arylation/cyclization of *ortho*-hydroxy-cinnamate ester derivatives with aryl iodides in water under aerobic conditions. Various 4-aryl coumarins derivatiate were synthesized conveniently in high to excellent yields. It is worthy to note that this method is distinguished by (1) readily available starting materials; (2) operational simplicity; (3) reaction in water; (4) air atmosphere; and (5) broad substrate scope. Further studies on the water-phase synthetic method are currently underway in our laboratory. Further elaboration of this novel one-pot strategy for the synthesis of other heterocyclic compounds is ongoing in our laboratory.

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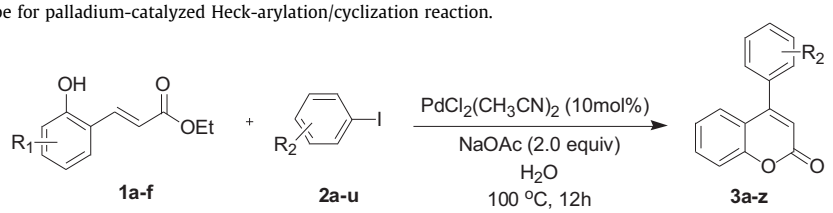
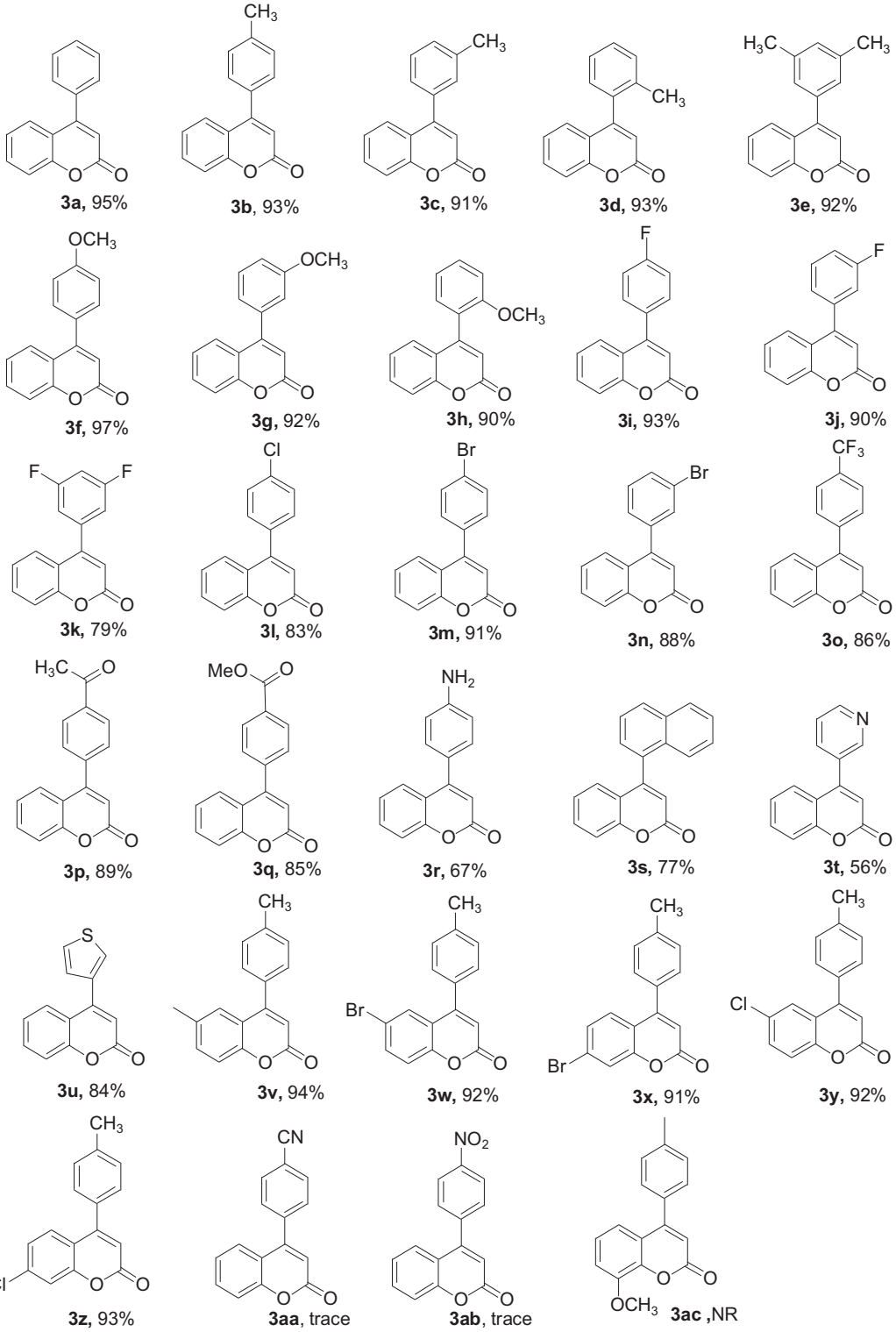
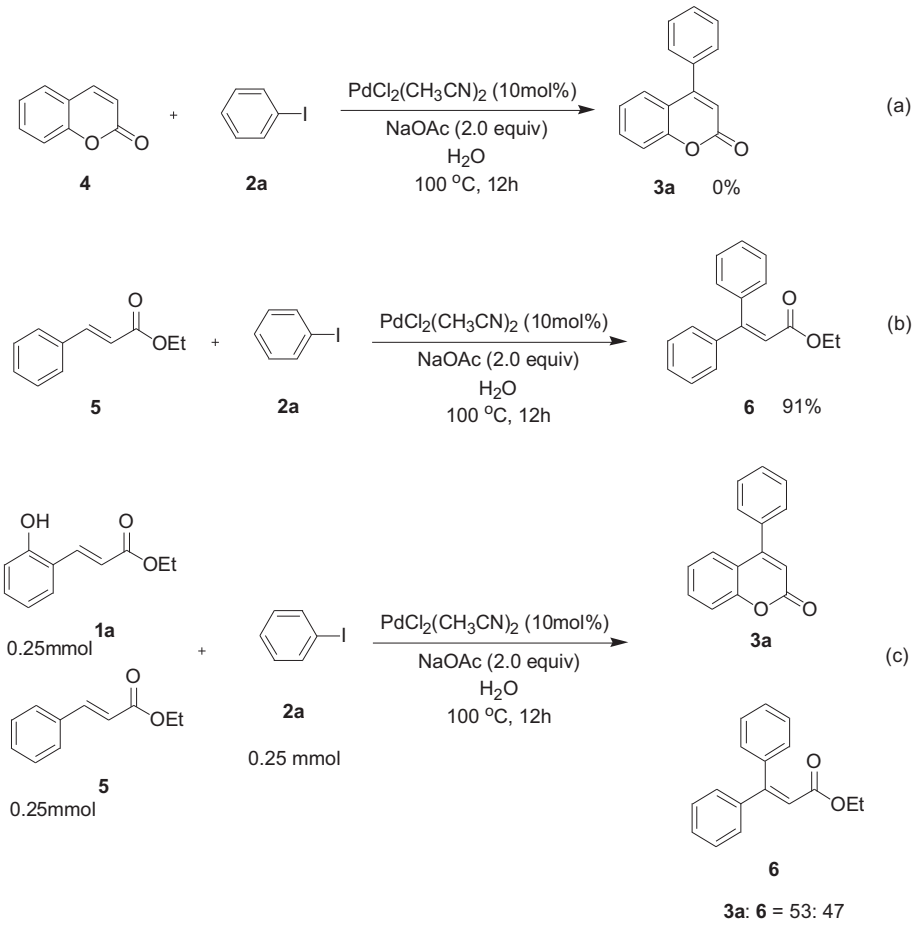
Table 2
Substrate Scope for palladium-catalyzed Heck-arylation/cyclization reaction.



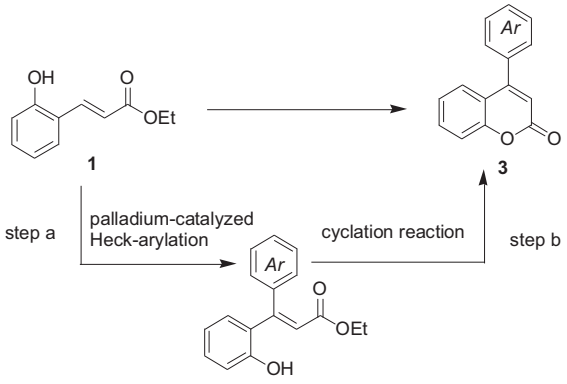
1a-f **2a-u** **3a-z**



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $PdCl_2(CH_3CN)_2$ (10 mol%), NaOAc (1.0 mmol), H_2O (1 mL), 100 °C, 12 h.



Scheme 2. Control experiments for plausible mechanism investigation.



Scheme 3. Proposed reaction pathway for the one-pot synthesis of 4-aryl coumarins.

Acknowledgements

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.05.032.

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