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COMMUNICATION

Metal-Free Regioselective C–H Chalcogenylation of Coumarins/(Hetero)Arenes at Ambient Temperature

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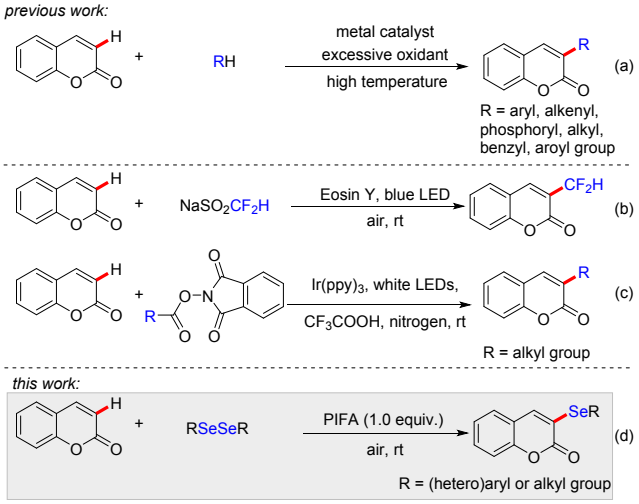
A novel, practical and metal-free approach for the regioselective selenation of coumarins employing (bis(trifluoroacetoxy)iodo)benzene (PIFA) at room temperature is presented. The developed method is suitable for a wide substrate scope and affords 3-selenyl coumarins in good to excellent yields with high selectivity. A radical mechanism is proposed for this new transformation. Furthermore, the application of sulfenylation with coumarines and selenation with other (hetero)arenes in this transformation is successful.

Coumarin and its derivatives are largely distributed in naturally occurring products and pharmaceuticals as key scaffolds, and they also play an important role in organic materials due to their optical activities.[1] Among a broad range of coumarin derivatives known, 3-substituted coumarins are recently drawing considerable attention since they exhibit a wide spectrum of biological activities, such as anti-inflammatory, antioxidant, anti-HIV, anticancer and antimicrobial.[2] On account of the important applications of 3-substituted coumarins in various fields, methods for synthesizing this type of compounds have been widely explored.

Coupling reactions with pre-functionalized reactants (coumarins or partners) are regarded as conventional procedures for the preparation of 3-substituted courmarins.[3] In recent years, direct C–H functionalization has emerged as a straightforward and atom-economical route in modern synthetic chemistry. On the basis of this strategy, a number of methods have been established for regioselective introduction of groups to the C3-position of coumarin skeleton via cross-dehydrogenative coupling (CDC). According to the mechanism, the reported protocols can be generally classified into two categories. One involves electrophilic attack of palladium species to the C3-position of coumarins (scheme 1a).[4] Normally, this type of reaction requires extra additives and ligands, and is used to synthesize 3-aryl coumarins, 3-alkenyl coumarins and 3-phosphoryl coumarins. The other one involves electrophilic attack of radicals to the C3-position of coumarins.[5] Metal catalysts (such as cobalt, copper, iron), excessive oxidants and high temperature are needed for this type of reaction to generate radicals. Different 3-alkyl coumarins, 3-benzyl coumarins and 3-aroyl coumarins were constructed by using these methods. Very recently, two elegant methods for the installment of difluoromethyl and alkyl groups to the C3-position of coumarins were achieved under photocatalysis at room temperature by Deng's group[6a] and Yang's group[6b], respectively (scheme 1b, 1c). Obviously, novel approaches for the regioselective formation of new bond, especially C–X bond at the C3-postion of coumarins under environmentally friendly reaction conditions are in high demand.



Scheme 1. Direct regioselective functionalization of coumarins at the C3-postion.

Selenium is a very important element in our body, selenium-containing compounds are widely distributed in bioactive compounds and natural products.[7] So far, a series of routes have been developed for the construction of C–Se bond using elemental selenium or non-elemental selenium as selenating reagents.[8,9] However, methods for the selenation of coumarins at the C3-position are rare. Only three protocols were reported, but they were limited to 4-substituted coumarins.[9] To the best of our

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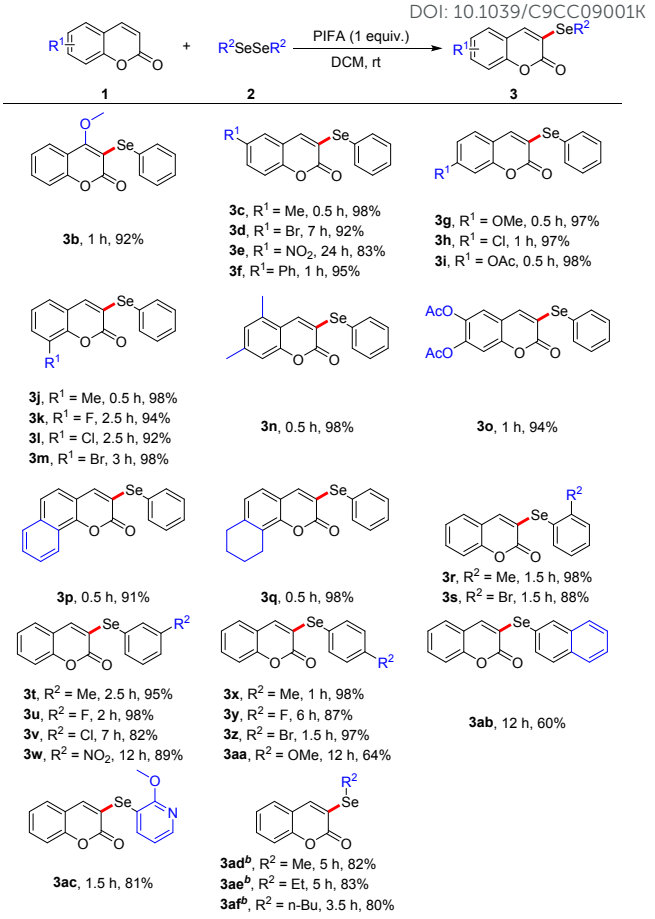
knowledge, direct regioselective selenation of coumarin skeleton at the C3-position has never been reported.

As part of our ongoing studies on the development of new approaches for the chalcogenylation of heterocyclic compounds,[8h,10] we are interested in the exploration of novel routes for the regioselective selenation of coumarin skeleton at the C3-position. In the past decades, several impressive methods with radical processes were reported for the direct incorporation of groups onto heterocycles by formation of C–C bond, using hypervalent iodine reagents as promoters.[11] These reactions were conducted at ambient room temperature, under metal-free conditions. Combining the applications of hypervalent iodine reagents in radical reactions and the aforementioned background of preparation of 3-substituted coumarins, it was envisioned that regioselective formation of C–Se bond could be accomplished by promotion of hypervalent iodine reagents via a radical process under environmentally friendly conditions. Herein, we wish to unveil a novel protocol for the PIFA mediated regioselective selenation of coumarins at the C3-position with diselenides at ambient temperature (scheme 1d).

We started our investigation focusing on the reaction between coumarin **1a** and diphenyl diselenide **2a**. Different solvents, oxidants, amounts of oxidants, equivalents of diphenyl diselenide were screened (see the ESI†, table 1). Finally, the optimal conditions for the regioselective selenation of coumarins at the C3-position were obtained: diphenyl diselenide (1.2 equiv.), PIFA (1.0 equiv.), in DCM (2 mL) at room temperature for 1 h (entry 11). Furthermore, a 10 mmol scale reaction was performed under the standard reaction conditions, and the desired product was obtained in 93% yield in 2 h (entry 13). The structure of product **3a** was further confirmed by single-crystal X-ray analysis (CCDC 1944304, see the ESI†).

Having identified the optimal parameters of the model reaction, the substrate scope and generality of this transformation were evaluated. Initially, coumarin derivatives bearing diverse electron-donating or -withdrawing groups at different positions of coumarin rings were tested with diphenyl diselenide under the standard reaction conditions. Generally, most of the reactions proceeded smoothly, giving the expected products in good to excellent yields in a short reaction time (table 2, **3b**–**3q**). It is worth mentioning that coumarin derivatives with halogens or ester groups were tolerated in this transformation, allowing subsequent elaboration of corresponding products at the remaining reactive sites (**3d**, **3h**, **3i**, **3k**–**3m**, **3o**). The electron-deficient nitro coumarin also gave the desired product in 83% yield in 24 h (**3e**). Furthermore, the reactions of diphenyl diselenide with 2*H*-benzo[*h*]chromen-2-one or 7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one worked well, affording the desired products in 91% and 98% yields, respectively (**3p**, **3q**). No reaction was observed when 3-methyl coumarin was used as a substrate, this result further proved the specific regioselectivity of this transformation. Subsequently, we turned our attention to investigate the scope of the reaction with respect to the diselenide reactants[8h,10a,12] with coumarin under the standard reaction conditions. Reactions of dipenyl diselenides with various substitutents (OMe, Me, F, Cl, Br, NO_2) at different positions of the phenyl ring worked well, and the desired products were obtained in good to excellent yields (**3r**–**3aa**). Moreover, the reaction proceeded smoothly with dinaphthyl diselenide, furnishing the desired product in 60% yield in 12 h (**3ab**). This protocol was also suitable for heterocyclic diselenide, the reaction of 1,2-bis(2-methoxypyridin-3-yl)diselane provided

Table 2 Selenation of coumarins and diselenides[a]

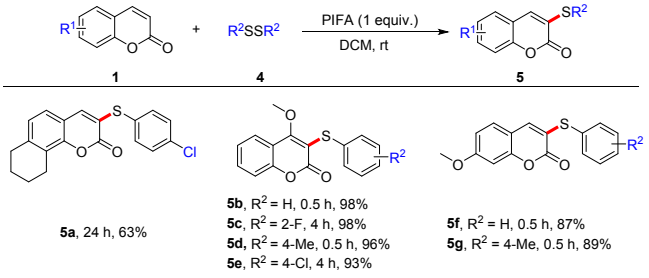


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), PIFA (1 equiv.), in DCM (2 mL) at room temperature in air. [b]3 equiv. of PIFA were used.

the desired product in 81% yield in 1.5 h (**3ac**). Due to the reactivity of alkyl selenides, reactions of selenation with dialkyl diselenides involving radicals are difficult. Interestingly, the application of dialkyl diselenides in this novel transformation was also successful, and the corresponding products were obtained in good yields (**3ad**–**3af**).

After successful development of this novel protocol, we wondered if this transformation is applicable for the direct regioselective sulfenylation of coumarins at the C3-position. Although many methods were reported for the direct regioselective formation of C–S bond at the C3-position of coumarins, all of them are limited to 4-hydroxyl

Table 3 Sulfenylation of coumarins and disulfides[a]



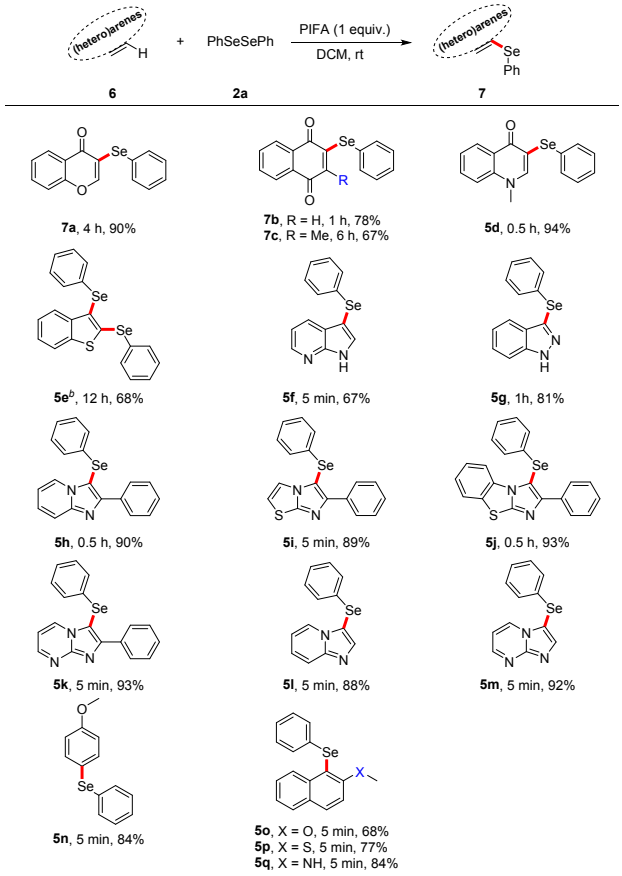
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), PIFA (1 equiv.), in DCM (2 mL) at room temperature in air.

coumarins.[9c,13] To our delight, this novel protocol is also suitable for the direct regioselective sulfenylation of coumarins at the C3-position, and the corresponding products were obtained in good to excellent yields (table 3, **5a**–**5g**).

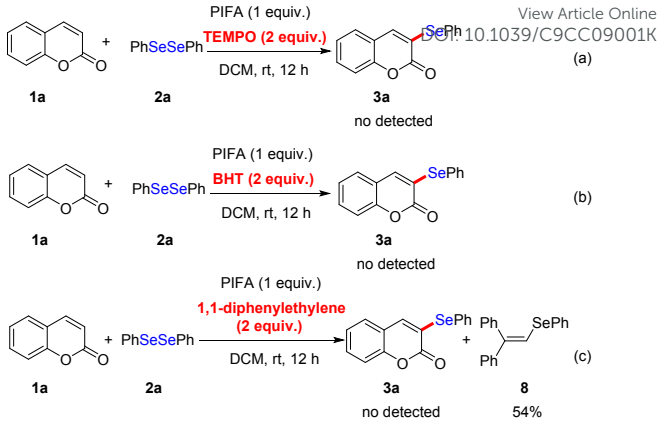
Gratifyingly, this method allows selenation of various (hetero)arenes with diphenyl diselenide under standard reaction conditions. Reactions of chromone, benzoquinones and 1-methylquinolin-4(1*H*)-one with diphenyl diselenide proceeded smoothly, the desired products were obtained in good to excellent yields (table 4, **7a**–**7d**). Diselenation occurred when benzo[*b*]thiophene was used as a substrate, and the corresponding product was obtained in 68% yield in 12 h (**7e**). The application of 7-azaindole and indazole in this transformation was successful, affording the desired products in 67% and 81% yields, respectively (**7f**, **7g**). Moreover, reactions of diphenyl diselenide with different imidazoheterocycles worked well, providing the desired products in good to excellent yields (**7h**–**7m**). This method was also suitable for C–H selenation of monocyclic and bicyclic arenes. When anisole was subjected to this protocol, the product **7n** was obtained in 84% yield in 5 min. Reactions of diphenyl diselenide with 2-methoxynaphthalene, methyl(naphthalen-2-yl)sulfane and *N*-methylnaphthalen-2-amine proceeded smoothly, giving the expected products in good yields in a short reaction time (**7o**–**7q**).

To gain some insights into the mechanism of this

Table 4 Selenation of (hetero)arenes and diphenyl diselenides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), PIFA (1 equiv.), in DCM (2 mL) at room temperature in air. [b]2.4 equiv. of **2a** were used.

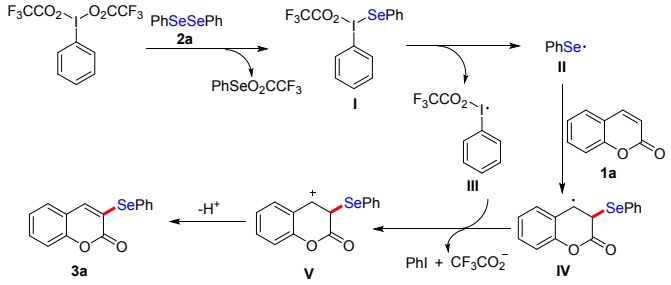


Scheme 2 Control experiments

unprecedented selenating route, we conducted the control experiments. Initially, radical trapping experiments of coumarin (**1a**) and diphenyl diselenide (**2a**) were examined in the presence of 2 equiv. of TEMPO (2,2,6,6-tetramethyl-1- piperidinyloxy) or BHT (butylhydroxytoluene) under the standard reaction conditions (Scheme 2a, 2b). After 12 h, no reactions were detected. These results suggested that this transformation might proceed by a radical pathway. In order to confirm the formation of selenyl radicals, a reaction was carried out under the standard reaction conditions in the presence of 2.0 equiv. of 1,1-diphenylethylene. After 12 h, no **3a** was observed; a new spot **8** was generated, it was confirmed as the adduct of selenyl radical and 1,1-diphenylethylene (scheme 2c).[14] Subsequently, reactions of all (hetero)arenes (**6a**–**6q**) with diphenyl diselenide (**2a**) were tried under the standard reaction conditions with 2 equiv. of TEMPO, BHT or 1,1-diphenylethylene. All of the reactions were suppressed, and the **8** was observed. These results indicated that the selenation of (hetero)arenes probably involved the selenyl radical.

On the basis of relevant reports[5,6,11,15] and our experimental results, a tentative mechanism for this novel transformation was proposed by taking coumarin **1a** and diphenyl diselenide **2a** as examples (scheme 3). Initially, reaction of PIFA with diphenyl diselenide provides intermediate **I**, which undergoes thermal homolytic cleavage to generate phenyl selenide radical **II** and radical **III**. Subsequently, electrophilic attack of radical **II** to **1a** produces intermediate **IV**. Oxidation of **IV** by **III** affords ationic intermediate **V**. Finally, deprotonation of **V** delivers the desired product **3a**.

In conclusion, an efficient and simple approach for



Scheme 3 Proposed mechanism

regioselective formation of C–Se bond at the C3-postion of coumarin skeleton is realized by using PIFA as a promoter at room temperature. Mild reaction conditions, good tolerance with different functional groups, broad substrate scope and short reaction time are the remarkable features of this transformation. Additionally, this protocol is suitable for the direct regioselective sulfenylation of coumarines at the C3-position and selenation of other (hetero)arenes. Further investigations into the applications of this new type of selenyl-coumarin compounds in synthetic chemistry and drug discovery are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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14 In scheme 2c, the reaction of coumarin and diphenyl diselenide was hampered by adding 1,1-diphenyl ethylene; the **8**, which was formed by the reaction of selenyl radical and 1,1-diphenyl ethylene, was isolated. These results suggested that the reaction might proceed via a radical process. In many reports, 1,1-diphenyl ethylene was added to reactions to confirm if the reactions involved radicals, such as: reference 6(a), 6(b).

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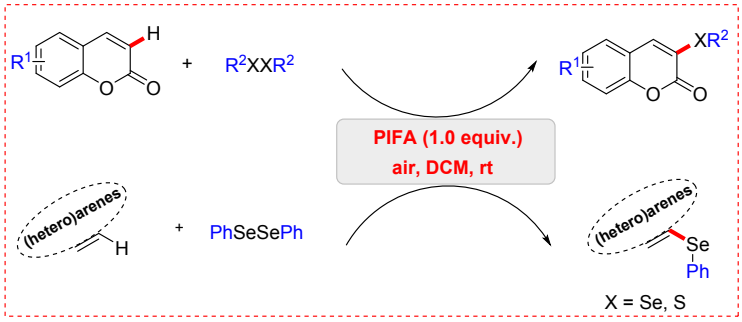

- Metal-free
- Mild reaction conditions
- Short reaction time
- 56 examples
- up to 98% yields

A novel and practical method for the direct regioselective selenation of coumarins at the C3-postion has been achieved using PIFA as a promoter at room temperature, this protocol is applicable for the direct regioselective formation of C–S bond at the C3-position of coumarins and selenation of other (hetero)arenes.