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Iron-catalyzed tandem reaction of C–Se bond coupling/selenosulfonation of indols with benzeneselenols†

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An iron-catalyzed tandem reaction of C–Se bond coupling/selenosulfonation was developed. Starting from sample indols and benzeneselenols versatile biologically active 2-benzeneselenonyl-1*H*-indoles derivatives were efficiently synthesized. The reaction mechanism was studied by the deuterium isotope study and *in situ* ESI-MS experiments. This protocol features mild reaction conditions, wider substrate scope and provides an economical approach toward C(sp²)–Se bond formation.

Due to the important applications in the preparation of synthetic materials,¹ pharmaceutical agents,² fluorescent probes,³ and functional organic materials,⁴ organoselenium compounds synthesis has attracted extensive attention from synthetic chemists. It is known that transition-metal catalyzed cross coupling reaction is the mostly used methodology for the incorporation of a Se atom into aromatic frameworks.⁵ However, prefunctionalization of the substrate is generally requested. Similar methods of C(sp²)–Se bonds formation have been scarcely described.^{6–8}

Comparative to the C(sp)–H, the C(sp²)–H bond activation need more harsh conditions and activated reaction systems.⁹ Considering the significance of diversifying synthetic strategies, our group focuses on transition-metal catalyzed C–H bond functionalizations.¹⁰ Herein, we report a novel iron-catalyzed direct C(sp²)–H bond activation/C–Se cross coupling reaction of indols with benzeneselenols. Versatile biologically active compounds 2-benzeneselenonyl-1*H*-indoles were efficiently synthesized in good to high yields. In this reaction, the inactive C(sp²)–H bonds were smoothly direct selenosulfonation under a moderate condition. At last, the reaction mechanism was studied by the deuterium isotope study and the *in situ* ESI-MS experiments.

At first, as shown in Table 1, the reaction conditions were screened based on the model reaction of indol **1a** with benzeneselenol **2a** (Table 1). The corresponding product structure of **3a** was confirmed by NMR spectrums. The iron catalysts displayed a good catalytic activity (entries 1–5). In addition, FeCl₃ exhibited superior catalytic efficiency over all of the examined iron catalysts (entry 5). These results indicated that DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and O₂ were the optimal base

and additive, which produced the product **3a** with an 83% yield (entry 14). It was also noted that the product yield was decreased when the reaction temperature was less or greater than 80 °C (entries 15 and 16). Furthermore, the results also show that the reaction yield of 1,4-dioxane as a solvent is higher than that of other solvents (entries 17 and 18). In particular, those reactions had to be carried out under a strict anhydrous condition. The presence of water would reduce the Fe³⁺ concentration, and reduced the catalytic activity (entry 19). Thus, the optimum reaction condition was determined as the **1a** and **2a** ratio of 1 : 1.5 in the presence of FeCl₃ (5 mol%), DBU (2 equiv.), at 80 °C for 10 hours (Table 1, entry 14).

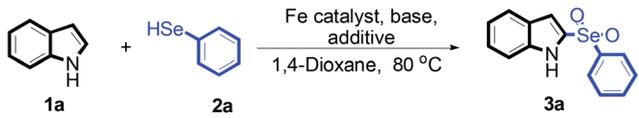
Next, the reaction scope was been screened, a wide array of indols **1** with benzeneselenols **2** were subjected to this reaction and given the products **3** in good to excellent yields (Table 2, 65–92% yield). It was found that both the electron-donating and electron-withdrawing indols derivatives **1** reacted smoothly with benzeneselenols **2**. Furthermore, indols **1** bearing electron-withdrawing groups showed better activity than bearing electron-donating groups. Benzeneselenols **2** bearing electron-donating groups showed better activity than bearing electron-withdrawing groups. To our delight, despite the electron-withdrawing effect of –NO₂ and –CF₃ group is so strong, the corresponding products **3h** and **3r** were still obtained in 75% and 69% yield (entries 8 and 9).

Furthermore, we next focused on evaluating the generality of tandem reaction of C–Se bond coupling/selenosulfonation by using a series of pyrroles. To our delight, *N*-methylpyrrole **4** with benzeneselenols **2** successfully provided the corresponding products **5** (Table 3, 59–79% yield). For both substrates, this reaction was amenable when electroneutral group (entry 1), electron donating group (entries 2 and 3), electron-withdrawing group (entry 4–8). Moreover, the trifluoromethyl substituted delivered the product **5h** exclusively in 59% yield which bearing of strong electron-withdrawing group. Furthermore, reactants

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Table 1 Optimization of the reaction conditions^a


Entry	Fe catalyst	Base	Additive	1a : 2a	Yield ^b (%)
1	FeCl ₂	DBU	O ₂	1 : 1	0
2	FeBr ₂	DBU	O ₂	1 : 1	0
3	Fe(OAc) ₂	DBU	O ₂	1 : 1	19
4	Fe ₂ (SO ₄) ₃	DBU	O ₂	1 : 1	23
5	FeCl ₃	DBU	O ₂	1 : 1	67
6	FeCl ₃	Imidazole	O ₂	1 : 1	36
7	FeCl ₃	Piperidine	O ₂	1 : 1	49
8	FeCl ₃	<i>N,N</i> -Dimethylaniline	O ₂	1 : 1	46
9	FeCl ₃	Tri- <i>n</i> -propylamine	O ₂	1 : 1	38
10	FeCl ₃	DABCO	O ₂	1 : 1	57
11	FeCl ₃	DBU	AgO	1 : 1	0
12	FeCl ₃	DBU	H ₂ O ₂	1 : 1	38
13	FeCl ₃	DBU	CH ₃ COOOH	1 : 1	42
14	FeCl ₃	DBU	O ₂	1 : 1.5	83
15	FeCl ₃	DBU	O ₂	1 : 1.5	65 ^c
16	FeCl ₃	DBU	O ₂	1 : 1.5	82 ^d
17	FeCl ₃	DBU	O ₂	1 : 1.5	64 ^e
18	FeCl ₃	DBU	O ₂	1 : 1.5	77 ^f
19	FeCl ₃	DBU	O ₂	1 : 1.5	23 ^g

^a Unless otherwise noted, reactions conditions were **1a** (0.5 mmol), **2a** (0.5 mmol), Fe catalyst (5 mol%), base (2 equiv.), additive (2 equiv or under atmosphere), 1,4-dioxane (4 mL), 80 °C for 10 h. ^b Isolated yield. ^c 70 °C. ^d 90 °C. ^e In CHCl₃. ^f In DMF. ^g Solvents not been dried.

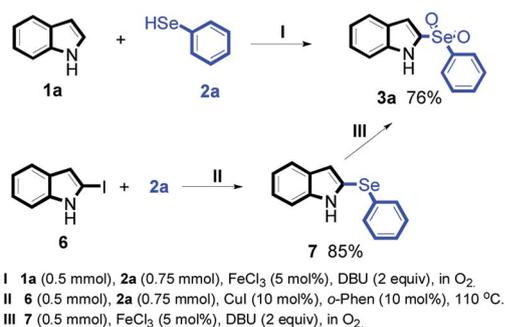
with more complex substituents also perform smoothly (entry 9). Both the results demonstrated the good generality and high functional group tolerance of this method.

To obtain the preliminary data of the mechanism, some addition reactions have been done (Scheme 1). At first, the model reaction (Scheme II) was conducted in two separate steps: the C–Se cross coupling reaction of **6** with **2a** given a product **7** (Scheme I, 85% yield).¹¹ Next, **7** was reacted under our standard conditions, the reaction successfully obtained the target product **3a** (Scheme III 79% yield), indicating that the intermediate **7** was involved in the reaction mechanism.

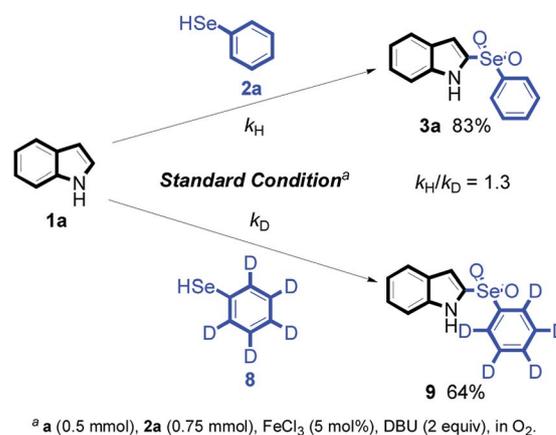
Next, we used isotope experiments to further study the reaction mechanism, as shown in Scheme 2. The kinetic deuterium isotope effects¹² observed in the control experiments

were indicated that the C(sp²)–H cleavage being the rate-limiting step ($k_H/k_D = 1.3$, for detail information please see ESI[†]).

Additionally, the model reaction mixture¹³ was subjected to the *in situ* ESI-MS analysis which the detection temperature was enacted at 120 °C (Scheme 3). The positive-ion mode ESI-MS showed a peak at 296.0 (*m/z*) which corresponding to [C₁₄H₁₁NNaSe]⁺. The peak at 328.0 was assigned to [C₁₄H₁₁NNaO₂Se]⁺ (Scheme 3a). Meanwhile, using the ¹⁸O₂ deuterium labeling study gave a peak at 331.9 was assigned to [C₁₄H₁₁NNa¹⁸O₂Se]⁺



Scheme 1 Preliminary data of the reaction mechanism.



Scheme 2 The kinetic deuterium isotope effects.



Table 2 Iron-catalyzed tandem reaction of C–Se bond coupling/selenosulfonation of indols with benzeneselenols^a

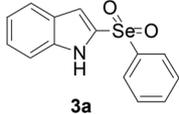
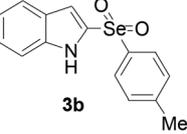
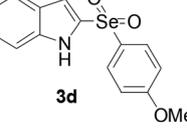
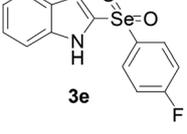
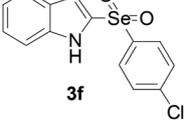
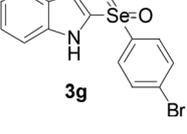
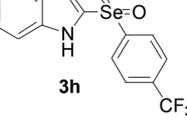
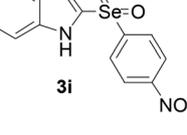
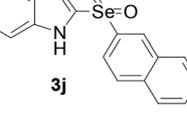
Entry	R	R ¹	3	Yield ^b
1	H	H		83
2	H	4-Me		84
3	H	4- <i>t</i> Bu		87
4	H	4-OMe		92
5	H	4-F		78
6	H	4-Cl		81
7	H	4-Br		83
8	H	4-CF ₃		75
9	H	4-NO ₂		69
10	H	Naphthyl		79



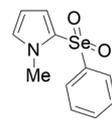
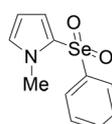
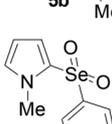
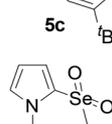
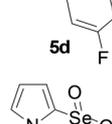
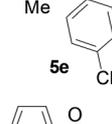
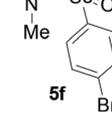
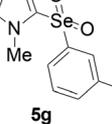
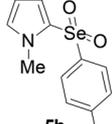
Table 2 (Contd.)

Entry	R	R ¹	3	Yield ^b
11	5-Me	4-Me		75
12	7-Me	4-Me		76
13	4-OMe	4-Me		74
14	5-OMe	4-Me		72
15	7-OMe	4-Me		67
16	4-OCH ₂ Ph	4-Me		66
17	6-Cl	4-Me		90
18	7-Cl	4-Me		91
19	3-Me	4-Me		65

^a Unless otherwise noted, reaction conditions were **1** (0.5 mmol), **2** (0.75 mmol), FeCl₃ (5 mol%), DBU (2 equiv.), under a O₂ atmosphere, 1,4-dioxane (5 mL), 80 °C for 10 h. ^b Isolated yield.

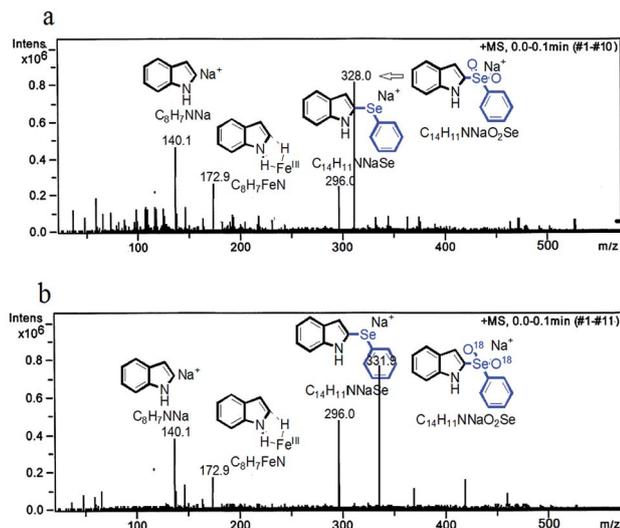


Table 3 Iron-catalyzed tandem reaction of C–Se bond coupling/selenosulfonation of *N*-methylpyrrole with benzeneselenenols^a

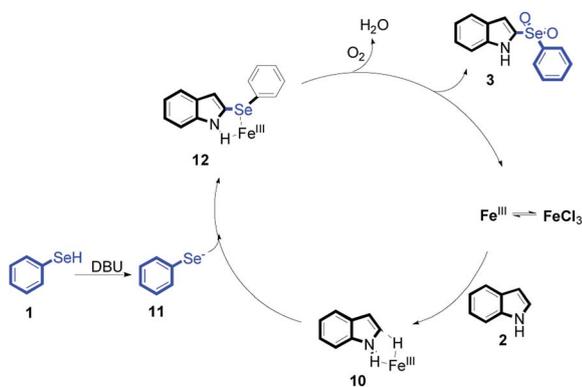
Entry	R ³	R ¹	5	Yield ^b
1	H	H		76
2	H	4-Me		79
3	H	4- <i>t</i> Bu		78
4	H	4-F		69
5	H	4-Cl		65
6	H	4-Br		66
7	H	3-Br		68
8	H	4-CF ₃		59
9	H	Naphthyl		70

^a Unless otherwise noted, reaction conditions were **4** (0.5 mmol), **2** (0.75 mmol), FeCl₃ (5 mol%), DBU (2 equiv.), under a O₂ atmosphere, 1,4-dioxane (5 mL), 80 °C for 10 h. ^b Isolated yield.





Scheme 3 The *in situ* ESI-MS spectras of iron-catalyzed direct C(sp²)-H bond activation/C-Se cross coupling (a) for the mode reaction, (b) for the ¹⁸O₂ deuterium labeling reaction.



Scheme 4 Proposed mechanism.

(Scheme 3b), also further validated the intermediate components hypothesis (For ESI HR-MS, please see ESI†).¹⁴

Based on these results, we proposed a possible reaction mechanism (Scheme 4). At the beginning of the reaction, the coordination process of Fe^{III} and reactant 2 generated an intermediate 10. Then, reactant 1 was converted to intermediate 11 by reacted with DBU. Next, intermediate 12 was provided from intermediate 10 with 11 *via* C-Se bond cross coupling. At last, through the oxidation reaction by O₂, intermediate 12 generated the desired products 3 and concomitantly formed a Fe^{III} intermediate, which re-entered the catalytic cycle.

Conclusions

In summary, we have reported an iron-catalyzed tandem reaction of C-Se bond coupling/selenosulfonation. Starting from sample indols and benzeneselenols versatile biologically active 2-benzeneselenonyl-1*H*-indoles derivatives were efficiently synthesized. The reaction mechanism was studied by the deuterium isotope

study and *in situ* ESI-MS experiments. This protocol features mild reaction conditions, wider substrate scope and provides an economical approach toward C(sp²)-Se bond formation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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