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Rose Bengal Catalysed Photo-Induced Selenylation of Indoles, Imidazoles and Arenes: A Metal Free Approach

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In this report, the highly efficient Rose Bengal-catalysed C(sp²)-H selenylation of indoles, imidazoles and arenes was achieved using a half molar equiv. of diorganoyl diselenides. This metal-free, photo-induced protocol resulted in the selenylated products in good to excellent yields. The reaction features are high yields, an atom-economic, gram-scalable and metal-free approach, and applicability to different biologically relevant (hetero)arenes.

The indole moiety is widely distributed in heterocyclic nitrogen compounds in nature.[1] It is used in pharmaceutical, biological and materials applications as well as in organic synthesis, representing an important "privileged scaffold".[1,2] Several commercially-available drugs and biologically important compounds (e.g. **1a-b**, Figure 1) have the indole motif in their core structure.[2e,3] Similarly, other related heterocyclic compounds and arenes are well-known for same properties.[4]

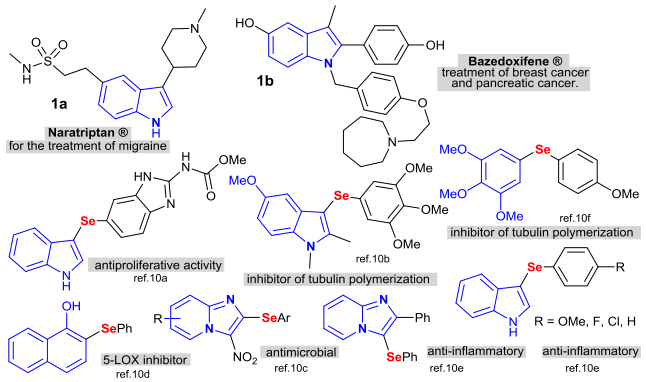


Figure 1. Biologically relevant indoles and selenylated arenes.

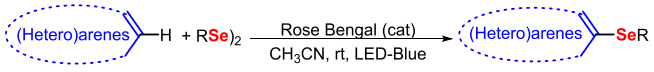
The biological and medicinal properties of organoselenium compounds are also receiving increasing attention.[5,6] In addition, these compounds play an important role in modern organic synthesis,[7,8] and in materials science.[9] Consequently, important advances have been made in the selective C–Se bond formation, and selenylation via C–H functionalisation is becoming an interesting approach.[7,8]

Considering the therapeutic properties of indoles, imidazoles and arenes, as well the biological relevance of organoselenium compounds, few synthetic methods for the preparation of selenyl-indoles, -imidazoles and -arenes (Figure 1) have been reported in the literature.[10] Generally, for the synthesis, metal (M) or metal-free (MF) approaches are used with conventional heating, microwave or ultrasound irradiation.[11,12] In spite of their good features, some of the methods described in the literature are associated with limitations in terms of sustainability, such as low atom economy, pre-functionalized coupling partners, and transition metal catalyst.

In recent years, photo-induced organic transformations have emerged as an attractive and suitable approach.[13]

Herein, we report, for the first time, the Rose Bengal-catalysed photo-induced synthesis of biologically important selenyl-indoles, -imidazoles and -arenes through C(sp²)-H bond selenylation, using diselenide (Scheme 1). This represents a continuation of our research lines, which encompass the design and development of eco-friendly processes and the chalcogenation of biologically relevant heteroarenes.[12i-k,14] During the preparation of this manuscript, a related study by Liu using an iridium complex as a photosensitizer appeared in the literature.[13i] Despite the features of this method, there is a need for an alternative and sustainable transition metal-free photo-induced approach for the selenylation of (*N*-hetero)arenes.

Our new sustainable, scalable, metal-free photo-induced approach worked effectively using indoles, imidazoles and arenes with a half molar equivalent of diorganyl diselenides (atom-economic reaction) in the presence or absence of air.



Scheme 1. Rose Bengal catalyzed selenylation

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The coupling reaction of indole **2a** and diphenyl diselenide **3a** was employed as a model reaction (Table 1). Preliminary tests were performed in DMF as the solvent using blue LEDs (415 nm) and applying various catalysts or catalyst-free conditions (entries 1-6). The reaction in the absence of a catalyst did not give any product (entry 1). Of the various photo-catalysts tested, Rose Bengal was the most efficient, affording the C(sp^2)-H bond selenylated product **4a** in 85 % yield (entry 5 *vs* 2-4,6). Next, the type of solvent was screened for this coupling reaction (entries 6-13) and acetonitrile provided the best result in terms of promoting the formation of **4a** (entry 7 *vs* 8-13). After ascertaining the best catalyst and solvent, we then evaluated the effect of the Rose Bengal catalyst loading (entries 14-16).

Changing the quantity of the catalyst from 5 to 6 mol % or 4 mol% did not have a notable effect on the yield (entries 14 and 15 *vs* 7). However, a further decrease in the catalyst loading to 3 mol% led to a decrease in the yield of **4a** (entry 16). Subsequently, the influence of the reaction time (entries 17-19) was examined and the optimum time was found to be 6 h (entry 18). Lastly, the effect of light on the reaction was monitored (entries 20-21). There was no reaction in the absence of light (entry 20), demonstrating the importance of the presence of a light source. We also observed that the reaction in the presence of white LED provided **4a** in 49% yield (entry 21), signifying the superiority of blue LED for this transformation

Table 1. Optimisation of reaction conditions.[a]

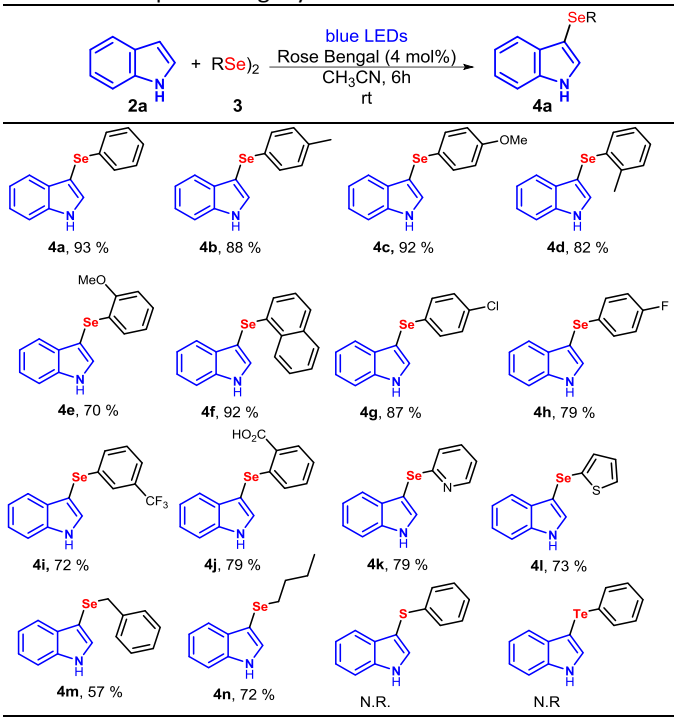
Entry	Catalyst (mol%)	solvent (2 mL)	Time (h)	Yield[b] (%)
1	-	DMF	24	N.R.
2	Eosin Y (5)	DMF	24	64
3	Eosin B (5)	DMF	24	40
4	Alizarin(5)	DMF	24	32
5	Rose Bengal (5)	DMF	24	85
6	Fluorescein (5)	DMF	24	71
7	Rose Bengal (5)	CH_3CN	24	93
8	Rose Bengal (5)	THF	24	25
9	Rose Bengal (5)	DCM	24	12
10	Rose Bengal (5)	EtOH	24	Trace
11	Rose Bengal (5)	Ethyl lactate	24	N.R.
12	Rose Bengal (5)	Toluene	24	Trace
13	Rose Bengal (5)	H_2O	24	N.R.
14	Rose Bengal (6)	CH_3CN	24	94
15	Rose Bengal (4)	CH_3CN	24	93
16	Rose Bengal (3)	CH_3CN	24	86
17	Rose Bengal (4)	CH_3CN	12	92
18	**Rose Bengal (4)**	**CH_3CN**	**6**	**93**
19	Rose Bengal (4)	CH_3CN	3	52
20[c]	Rose Bengal (4)	CH_3CN	6	N.R.
21[d]	Rose Bengal (4)	CH_3CN	6	49

[a]Reaction conditions: **2a** (0.25 mmol), **3a** (0.125 mmol), catalyst (mol %), solvent (2 mL),. [b]Isolated yields. [c] Reaction in dark. [d] Reaction in the presence of white LED .

After ascertaining the best reaction parameters (Table 1, entry 18), the generality and scope of the C(sp^2)-H bond selenylation of other indoles **2** with various diorganyl diselenides **3** were investigated (Schemes 2 and 3). We first evaluated the efficiency of different diorganyl diselenides **3** while keeping indole **2a** constant (Scheme 2).

The reaction worked efficiently for structurally diverse diselenides **3**. Various substituted diselenides **3**, i.e., electron-donating (EDG, R = Me, OMe) and electron-withdrawing (EWG, R = F, Cl, CF_3) groups as well as a bulky group, i.e., naphthyl, successfully afforded the corresponding selenylated products **4a-i** in excellent yields (86%-94%). The system tolerated the electronic effects of the substituents at the *para* position on the phenyl group of diselenides **3** (**4a-c,g-h**). Furthermore, a weaker influence was observed due to the steric hindrance of *ortho*-substituted aryl diselenides as compared to the respective *para* derivatives (**4b-c** *vs* **4d-e**). However, in the case of sterically-hindered and bulkier substrates (1-napthyl), the selenylated product **4f** was obtained in 92% yield. To our delight, when diselenide with 2-caboxylic acid **3j** was used as the substrate (an important moiety for further transformations), the desired product **4j** was isolated in 79 % yield. In addition, in the case of dibutyl- and dibenzyl-diselenides the butylated and benzylated products **4n-m** were obtained in 72% and 57% yields, respectively. Interestingly, it was observed that the C-2 heteroaryl diselenide provided the desired selenides **4k-l** with 79% and 73% yields, respectively. Lastly, when diphenyl ditelluride and disulphide were tested under the optimized reaction conditions, no reaction was observed.

Scheme 2. Scope of diorganyl diselenides **3**.[a]



[a] Isolated yield.

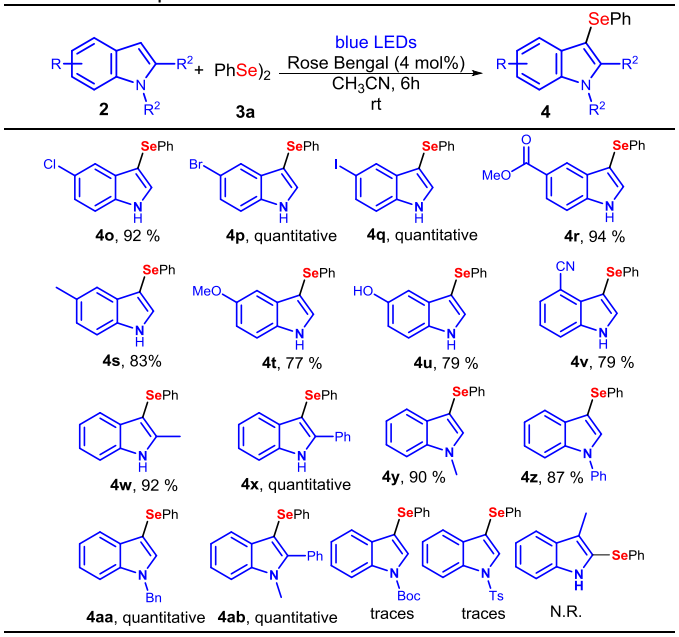
To check the versatility of this protocol and broaden the scope in relation to the substrate, the influence of various indole cores **2** was evaluated with diselenide **3a** (Scheme 3).

Indoles **2**, with different functionalities attached at the C-5 position of the aryl moiety, were tested, affording **4o-u** with 77% to quantitative yields. In general, EWG (R = Cl, Br, I, CO_2Me) were better than the EDG (R = Me, MeO, OH). In the case of the substituted indoles 5-Br and 5-I, the reaction afforded the selenylated products **4p-q**, quantitatively, while the nitrile substituted indole at the C-4 position resulted in the desired product **4v** in 79% yield.

We further extended our study with the variation of substituents at the C-1 and C-2 positions of the indoles, which modulated the performance of the selenylation reaction. For example, the 2-methyl and 2-phenyl substituted derivatives of indole resulted in the corresponding 3-selenyl-indoles **4w-x** in 92% and quantitative yield, respectively. Nitrogen substituted indoles, such as 1-methyl, 1-benzyl and 1-phenyl indoles afforded the selenylated products (**4y-z,aa**) in excellent yields. Moreover, the reaction also tolerated a 1,2-disubstituted indole, furnishing the product **4ab** quantitatively.

However, the reaction failed when *N*-Boc and *N*-Ts were used as substrates. Similarly, when 3-methyl indole was employed as the substrate, under the optimized conditions, no reaction was observed.

Scheme 3. Scope of indole **2**.[a]



[a] Isolated yield.

In order to demonstrate the effectiveness of this new photo-induced protocol, a number of reactions were performed on various scales. Indole **2a** efficiently reacted with diselenide **3a** under the optimized reaction conditions up to a 10 mmol scale, affording the coupled product **4a** with no major decrease in yield (Figure 2). Therefore, this procedure represents a practical method for the synthesis of selenium containing biologically relevant lead compounds.

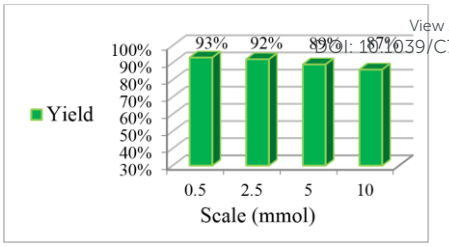
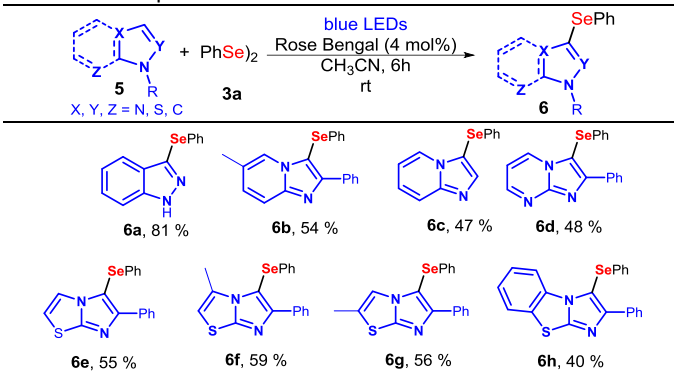


Figure 2. Results for the scale-up reactions.

Encouraged by the results of this metal-free photo-induced selenylation of indoles, we extended this method to other *N*-heteroarenes **5** under the ideal reaction conditions (Scheme 4). Indazole **5a** resulted in the corresponding C-3-selenylated product **6a** in good yield. Imidazo[1,2-*a*]pyridines **5b-5c** and imidazo[1,2-*a*]pyrimidine **5d** furnished the coupled product **6b-d** in 47-54% yields. Furthermore, imidazo[2,1-*b*]thiazoles **5e-h** were tested as the substrate for selenylation, resulting in **6e-h** in 40-59% isolated yields.

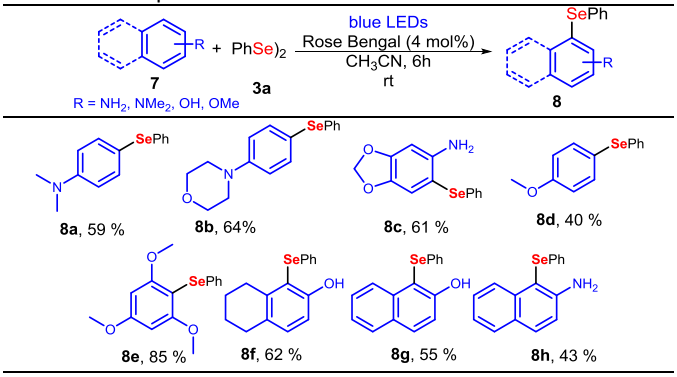
Scheme 4. Scope of *N*-heteroarenes **5**.[a]



[a] Isolated yield.

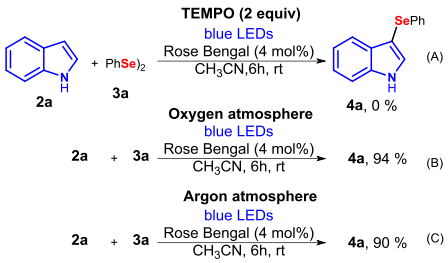
Following the success in the Rose Bengal-catalysed, photo-induced C(sp^2)–H bond selenylation of indole **2a** and other *N*-heteroarenes **5**, this method was extended to substituted mono-cyclic/ bicyclic arenes **7** and diphenyl diselenide **3a** as the coupling partner (Scheme 5). To our delight, the reaction furnished the desired selenylated products **8a-h** in moderate to very good yields.

Scheme 5. Scope of *N*-heteroarenes **5**.[a]



[a] Isolated yield.

In view of the unique features observed in this new coupling reaction and to gain some insight into the mechanism involved in the Rose Bengal-catalysed selenylation of indoles and other arenes through C(sp²)–H selenylation, some control experiments were carried out (Scheme 6). In the case of a radical inhibitor (TEMPO), the reaction was completely inhibited (Scheme 6A), indicating the involvement of radical species in this transformation. When the optimal reaction was performed under an oxygen atmosphere instead of open air, there was no effect on the yield (Scheme 6B), indicating that O_2 could be involved in the reaction pathway. Similarly, when the reaction was carried out under an argon atmosphere, no major effect was observed (Scheme 6C), indicating that the reaction follows a different route in an argon environment.



Scheme 6. Control experiments.

In order to investigate the effect of photo-irradiation, an experiment with visible light switched on-off was performed. The graph (Figure 3) indicates that for this coupling reaction a continuous supply of light is required. Furthermore, this result also indicates that radical-chain propagation is not a key pathway in the Rose-Bengal catalysed selenylation of indoles.

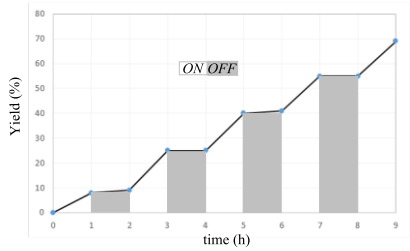
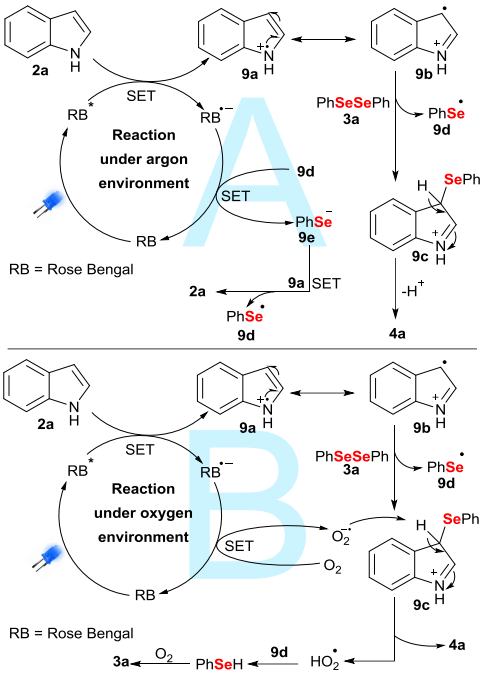


Figure 3. Switch on/off experiments.

Based on these results and reports in the literature,[13f,h,j] two plausible mechanisms for this transformation can be proposed (Schemes 7A and 7B), in argon and in oxygen environments, respectively. Under argon atmosphere (Scheme 7A), the Rose Bengal (RB) photocatalyst was excited by visible light irradiation to RB*, which through a single electron transfer (SET) with indole **2a** generates $RB^{\bullet-}$ and **9a-b**. The indole $\mathbf{9a}^{\bullet+}$, through the species **9b**, would react with diselenide **3a**, generating the selenylated indole cation **9c** and $PhSe^{\bullet}$ **9d**. Deprotonation of the cation **9c** would furnish the desired product **4a**. $RB^{\bullet-}$ would transfer an electron to **9d** to generate **9e** and RB. The phenylselenium anion **9e**, through a SET with **9a**, would generate the indole **2a** and **9d**.

In the case of an oxygen atmosphere (Scheme 7B), the anion radical of O_2 ($O_2^{\bullet-}$), which is produced in the photocatalytic cycle of RB through a SET, would abstract a proton from **9c**, which would generate the desired product **4a** and perhydroxyl radical ($HO_2^{\bullet}$). The transfer of $H^{\bullet}$ from $HO_2^{\bullet}$ to **9d** would generate **3a** through PhSeH.



Scheme 7. Plausible Mechanism.

Conclusions

In summary, we have developed a Rose Bengal-catalysed, photo-induced, greener, regioselective and efficient strategy for the preparation of selenyl-indoles, -imidazoles and -arenes, through direct C(sp²)-H bond selenylation. Under optimized reaction conditions, this simple, metal-free approach worked well in the presence of a half equivalent of diorganyl diselenides (atom-economic reaction). This is an important contribution considering the potential therapeutic application of these compounds.

The features of this sustainable and robust catalytic protocol are: (1) metal-free; (2) photo-induced at room temperature; (3) atom-economic; (4) gram-scalable; (5) economical catalyst; (6) regioselectivity; and (7) applicable to a wide range of indoles, imidazoles and arenes.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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