

Metal-Free C-Se Cross-Coupling Enabled by Photoinduced Intermolecular Charge Transfer

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Metal-free C-Se cross-couplings via the formation of electron-donor-acceptor (EDA) complexes have been developed. The visible-light induced reactions can be applied for the synthesis of a series of unsymmetrical diaryl selenides employing aryl bromides, aryl iodides as well as aryl chlorides under mild reaction conditions. The scale-up was readily achieved. UV-Vis spectroscopy measurements provide insight into the reaction mechanism.

Aryl and heteroaryl selenides represent an important class of organic compounds due to their application in the fields of pharmaceuticals, agrochemicals and materials (Figure 1).¹⁻⁷ As a consequence, the development of methods to access such compounds is highly sought-after. Among the developed strategies, palladium-⁸⁻¹⁰ or copper-¹¹⁻¹³ catalyzed selenylation reactions of aryl halides play an important role in the construction of unsymmetrical diaryl selenides due to their high efficiency. However, the necessity of a transition-metal catalysts, strong bases, or high temperature limits the application of these protocols to a certain extent (Scheme 1a).

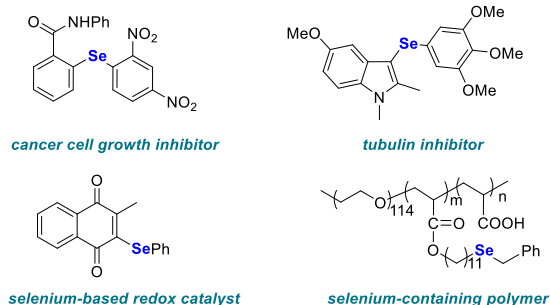


Figure 1. Examples of selenium-containing bioactive molecules, catalysts, and polymers.

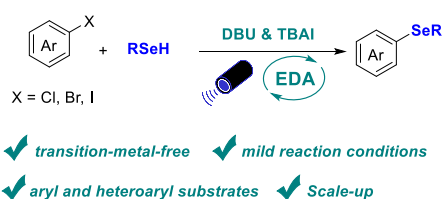
In recent years the use of the electron donor-acceptor (EDA) complex concept has led to the development of efficient cross-coupling reactions.¹⁴⁻¹⁶ In these cases, the stoichiometric electron-rich substrates (donors) and electron-deficient substrate (acceptors) form complexes in the ground state and these complexes can undergo intermolecular single-electron transfer (SET) upon irradiation with light.¹⁷⁻²¹ For instance, hydroimination cyclization products have been prepared via the EDA complex of dinitro-substituted *O*-aryl oximes and trimethylamine as demonstrated by

Leonori and coworkers.²² Also, Miyake and coworkers realized the C-S bond formation via the EDA complex between electron-poor aryl halide and electron-rich thiolate anion.¹⁸ A C-N bond cross-coupling was realized by König and coworkers via the generation of an EDA complex between electron-poor (hetero)aryl halides and anilines.²³ In addition, by employing the EDA strategy, Aggarwal and coworkers realized deoxygenative borylation reaction of 2-iodophenylthionocarbonates; thus converting efficiently aliphatic alcohols into boronic esters.²⁴ Furthermore, a decarbonylative arylation of redox-active esters as well as the trifluoromethylthiolation of aldehydes have been achieved by Molander and coworkers via photoactive EDA complexes.²⁵⁻²⁷

(a) Traditional transition-metal-catalyzed selenylation of aryl halides



(b) **This work:** Photoinduced metal-free C-Se cross-coupling



Scheme 1. Currently available selenylation processes and the newly developed C-Se cross-coupling.

In addition to these advances using stoichiometric reagents, new developments are being made in EDA catalysis. Pioneering work has been performed by Fu, Shang, and coworkers who realized the alkylation of silyl enol ethers, *N*-heteroarenes, and alkenes via EDA complex formation employing catalytic amount of sodium iodide and triphenylphosphine.²⁸ Furthermore, catalytic amounts of $B(C_6F_5)_3$ were applied in the oxidative C-S cross-coupling reaction of

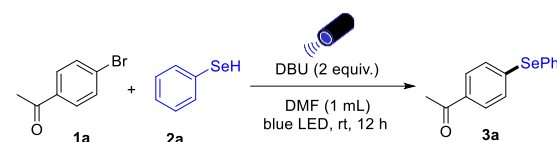
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thiophenol with indoles.²⁹ Considering the advantages of the EDA concept and the demand for general methods to construct diaryl selenides, we decided to investigate a metal-free C-Se bond cross-coupling enabled by photoinduced intermolecular charge transfer (Scheme 1b). We here describe the development of such metal-free C-Se bond forming reaction, the scale-up and mechanistic investigations to gain insight into the reaction mechanism.

We started to explore the photoinduced selenylation reaction of aryl halides by choosing 4-bromo-acetophenone **1a** as a model substrate in reaction with benzeneselenol **2a** (Table 1). After evaluation of the reaction parameters promising results were obtained by applying two equivalents of DBU as the base, DMF as the solvent, and 440 nm blue LED as light source (entry 1). Further optimization showed that the use of 390 nm purple LED resulted in lower yield (entry 2). Application of bases including K₃PO₄ and Cs₂CO₃ gave slightly lower yields (entries 3 and 4). Solvents such as DMA and DMSO resulted in decreased yield, while the use of MeCN improved the yield to 82% (entries 5-7). Moreover, the addition of 10 mol% of TBAI as an additive is beneficial for the transformation (entry 8).³⁰⁻³¹

Table 1. Optimization of the photoinduced selenylation reaction of aryl bromides.^a



Entry	Variables	Yield (%) ^b
1	none	75
2	390 nm purple LED	65
3	K ₃ PO ₄ as base	70
4	Cs ₂ CO ₃ as base	72
5	DMA as solvent	68
6	DMSO as solvent	30
7	MeCN as solvent	82
8	10 mol% TBAI, MeCN as solvent	90
9 ^c	0.5 mL MeCN	70
10 ^c	2 mL MeCN	82
11 ^c	20% light intensity	65
12 ^c	75 °C	73
13 ^c	1% V(H ₂ O)/V(MeCN)	76
14 ^c	under air	0
15 ^c	w/o DBU	0
16 ^c	w/o blue LED	0

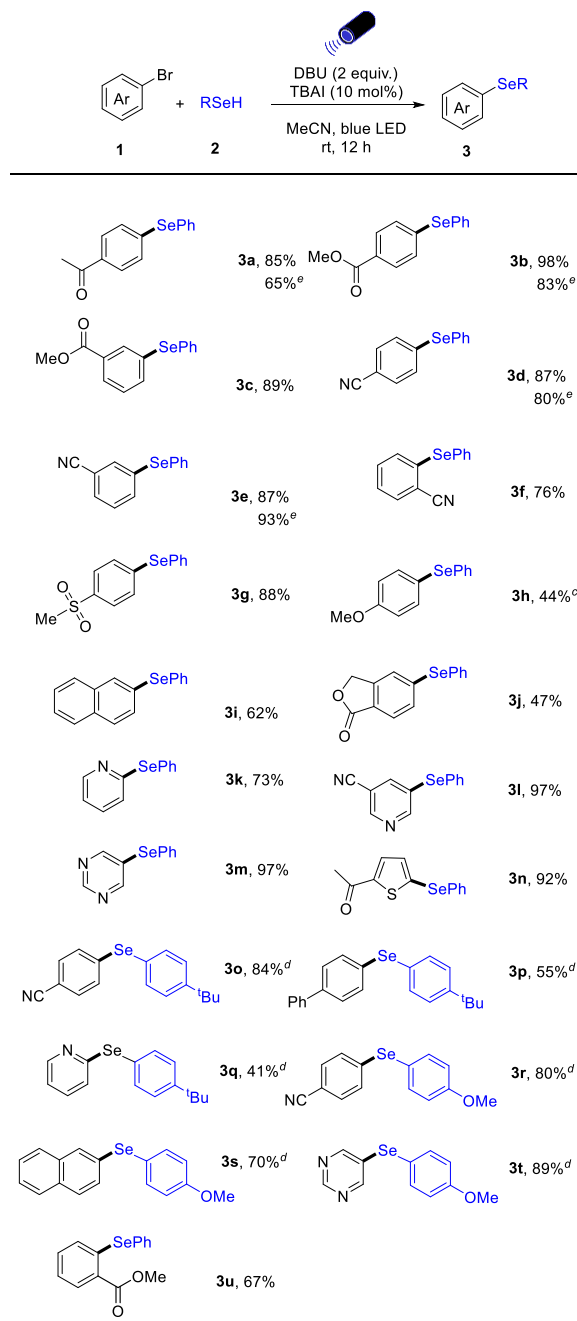
^aReaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), DBU (2 equiv.) in DMF (1 mL) was irradiated under 440 nm blue LED at rt. for 12 h. ^bGC Yields using dodecane as internal standard.

^cReaction conditions as entry 8.

Adjusting concentration, decreasing light intensity, elevating the temperature or adding water as additive led to lower yields (entries

9-13). The reaction gave no product when performed under air (entry 14). Control experiments showed that both, light and base are essential for the success of the reaction (entries 15 and 16).

Table 2. Scope of the selenylation reaction.^{a, b}

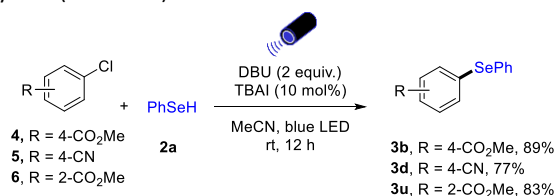


^aReaction conditions: Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), DBU (2 equiv.), TBAI (10 mol%) in MeCN (1 mL) was irradiated under 440 nm blue LED at rt. for 12 h. ^bYield after purification. ^c4-iodoanisole, 390 nm LED and 2 equiv. Na^tOBu was used. ^dThe reaction was performed on 0.10 mmol scale using the corresponding selenolate without the addition of DBU. ^eAryl iodides were used.

With the optimized reaction conditions in hand, the scope with respect to the aryl bromides was first explored (Table 2). A series of aryl halides bearing electron-withdrawing and electron-donating groups could be converted into the corresponding diarylselenide products. Functional groups including ketone, ester, cyano, sulfone as well as ether moieties are all tolerated in this photoinduced selenylation reaction (**3a-3h**). It is noteworthy that *ortho*-, *meta*-, and *para*-substituted aryl bromides all gave the corresponding products in high yields (**3b-3f**, and **3u**). Also, π -extended naphthyl bromide and the bicyclic aryl bromide underwent this transformation effectively (**3i** and **3j**). For electron-rich substrates (**1h**), the use of iodo-surrogates and 390 nm light source was found to be beneficial.

Importantly, pharmaceutically relevant heteroaryl bromides bearing pyridine, pyrimidine, thiophene reacted well in this catalytic system, affording the heteroaryl selenides in good to excellent yields (**3k-3n**). In addition, other sodium aryl selenolates could be applied in the reaction with both aryl- and heteroaryl bromides (**3o-3t**).

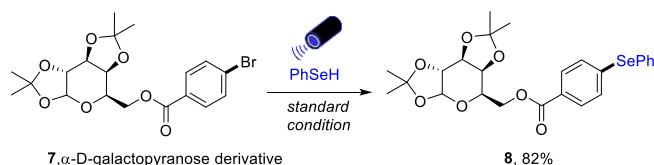
Moreover, our catalytic protocol can also be applied to aryl chlorides. *Para*-, *ortho* ester- and *para* cyano-substituted aryl chlorides could be converted to the corresponding unsymmetrical diaryl selenides in high yields (Scheme 2).



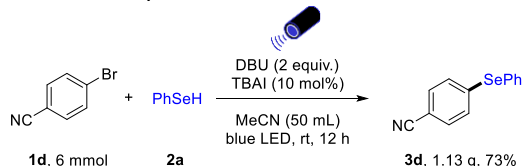
Scheme 2. Selenylation of aryl chlorides.

Furthermore, the effectiveness of this newly developed methodology is illustrated by the transformation of α -D-galactopyranose derivative **7** to the corresponding selenide **8** (82% yield, Scheme 3a). Furthermore, a gram-scale reaction with aryl bromide **1d** was successfully performed in 73% yield, demonstrating the practicality of this metal-free selenylation protocol (Scheme 3b).

a. Selenylation reaction of natural derived aryl bromide



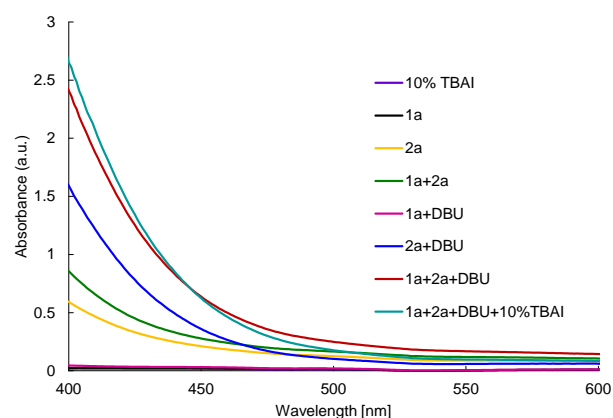
b. Gram-scale selenylation reaction



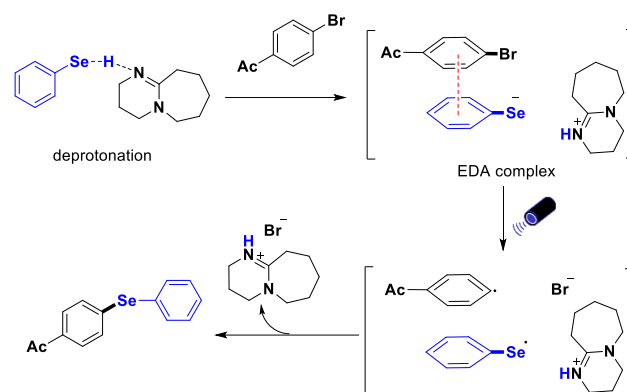
Scheme 3. Selenylation of the nature-derived substrate and gram-scale reaction.

To further understand the C-Se cross-coupling mechanism, UV-Vis absorption spectra of mixtures **1a**, **2a**, and DBU in MeCN (path length = 1 cm) were measured at concentrations of 0.1 M (Scheme 4a). The absorption of selenol **2a** increased considerably in the 400-475 nm region upon the addition of DBU, and the colour of the mixture of **2a** and DBU turned to light yellow. Also, the subsequent addition of 4-bromo-acetophenone **1a** to the mixture resulted in a stronger absorption, and the colour became orange, indicating an EDA complex is formed between **1a** and deprotonated **2a**. The addition of 10% TBAI slightly enhanced the absorption of the mixture. Based on these results, the mechanism was proposed as follows (Scheme 4b): **1a** and deprotonated **2a** first forms the EDA complex. Upon the visible light irradiation, the intermolecular charge transfer event happened between the EDA complex from thiolate anion to the aryl halide, generating selenyl radical, aryl radical, and halide anion. The diaryl selenide forms via radical-radical cross-coupling with the release of an ammonium salt.

a. UV-vis absorption spectra of mixtures **1a**, **2a**, and DBU in MeCN (path length = 1 cm) at concentrations of 0.1 M for each species.



b. Proposed mechanism for the photoinduced metal-free C-Se cross-coupling



Scheme 4. UV-vis absorption study and proposed mechanism.

In conclusion, a mild and efficient visible-light method for C-Se bond formation has been developed. The new protocol proceeds via a photoinduced intermolecular charge transfer between the EDA complex of aryl halide, selenol, and base. The practicality of this metal-free selenylation methodology is illustrated by the broad substrate scope, the late-stage functionalization of more complex

molecules, and the successful gram-scale reaction. UV-vis absorption spectroscopy measurements reveal that EDA complexes are involved in this process. The catalytic protocol is a general, metal-free, and low-cost alternative to transition-metal-catalyzed C-Se bond cross-coupling reactions and, thus, should find use in applications in which metal impurities are detrimental.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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