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# Three-Component Aminoselenation of Arynes

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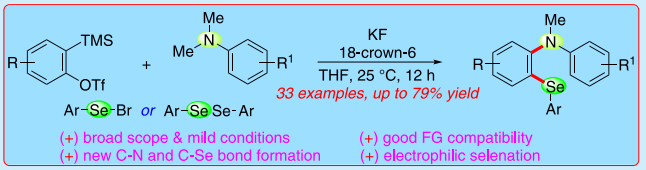
Supporting Information

**ABSTRACT:** The three-component coupling of tertiary amines, arynes, and aryl selenium bromide or diaryl diselenide as an electrophilic selenium source allowing the synthesis of 2-selanyl aniline derivatives is reported. This aminoselenation reaction of arynes installs a C−N and C−Se bond under mild conditions, and the products are formed in moderate to good yields. This reaction is compatible with various functional groups, and the preliminary studies on the mechanism of the reaction is also provided.




Organoselenium compounds are important structural motifs present in a variety of biologically active molecules and pharmaceuticals, and hence this class of compounds has gained much attention in recent years.[1,2] Among these compounds, the diaryl selenides are associated with interesting biological properties. For instance, the diaryl selenide **A** could be used as a human breast cancer cell growth inhibitor, **B** is useful as a thioredoxin reductase (TR) and glutathione reductase (GR) inhibitor,[3] and **C** can serve as an antitumor agent (Figure 1).[4] Moreover, the 2-substituted 1-naphthol **D** is a potent 5-lipoxygenase inhibitor,[5] the carboxylic acid **E** is a retinoic acid receptor (RAR) agonist, which is ∼10 times more powerful than its sulfur analogue,[6] and the 4-substituted quinoline **F** possesses antioxidant properties.[7] Given the biological significance of functionalized diaryl selenides, synthesis of this class of compounds is highly desirable.

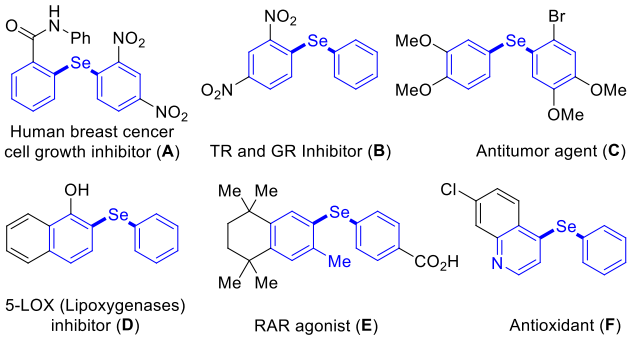
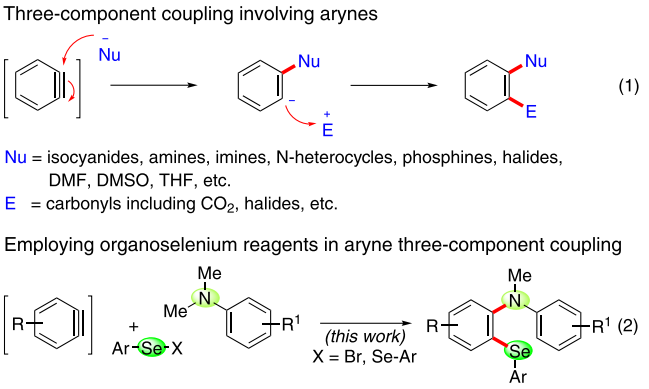



**Figure 1.** Selected biologically active organoselenium compounds.

During the course of our studies on three-component coupling employing arynes,[8,9] we recently envisioned that the use of organoselenium reagents as the electrophilic third component could result in the synthesis of functionalized diaryl selenides. A series of nucleophiles can trigger aryne three-component reactions (Scheme 1, eq 1).[8g,9a] Although various electrophiles such as carbonyl compounds including $CO_2$,[10,11] activated imines,[12] and halides[13] are known as electrophilic third components, the use of organoselenium reagents to intercept the in situ generated aryl anions in aryne three-component coupling, to the best of our knowledge, is unknown.[14] Herein, we report the three-component coupling of tertiary amines, arynes, and aryl selenium bromide or diaryl diselenide as an electrophilic selenium source, the aminoselenation reaction of arynes resulting in the formation of 2-selanyl aniline derivatives (eq 2).[15]

**Scheme 1. Aryne Three-Component Coupling**




We have recently reported the aryne three-component coupling triggered by aromatic tertiary amines using aldehydes, activated ketones, or $CO_2$ as the electrophilic third component.[16,17] Inspired by the aryne three-component coupling initiated by tertiary amines and given the biological importance of diaryl selenides, the present study was initiated by the treatment of aryne generated in situ from the 2-(trimethylsilyl)aryl triflate **1a**[18] (using KF and 18-crown-6) with *N*,*N*-dimethylaniline **2a** and phenyl selenyl bromide **3a** in THF at 25 °C. To our delight, under these conditions, the 2-selanyl aniline derivative **4a** was formed in 55% yield along

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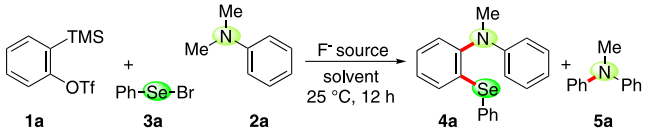
with the *N*-arylated product **5a** in 18% yield (Table 1, entry 1).[19] The desired product **4a** and the side product **5a** were

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | F⁻ source | solvent | yield of **4a** (%)[b] | yield of **5a** (%)[b] |
|---|---|---|---|---|
| 1 | KF/18-crown-6 | THF | 55 | 18 |
| 2 | KF/18-crown-6 | DME | 48 | 16 |
| 3 | CsF | $CH_3CN$ | <5 | <5 |
| 4 | TBAF | THF | <5 | <5 |
| 5[c] | KF/18-crown-6 | THF | 27 | 29 |
| 6[d] | KF/18-crown-6 | THF | 16 | 38 |
| 7[e] | KF/18-crown-6 | THF | 51 | <5 |
| 8[f] | KF/18-crown-6 | THF | 72 | <5 |

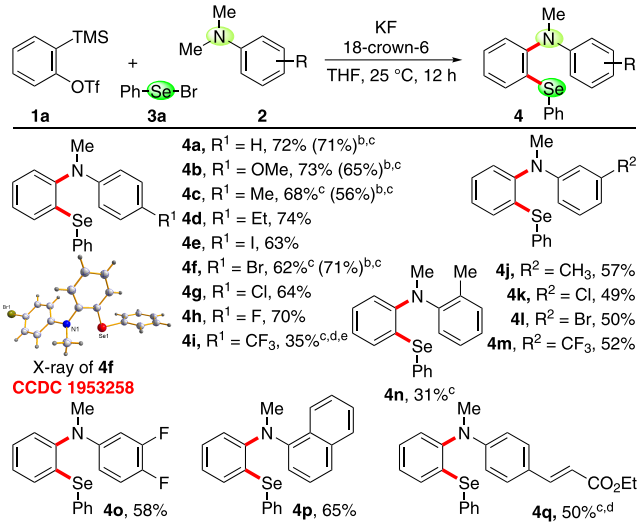
[a]Standard conditions: **1a** (0.30 mmol), **2a** (0.25 mmol), **3a** (0.25 mmol), fluoride source (2.4 equiv), solvent (1.0 mL), 25 °C and 12 h. [b]Yield of the isolated product. [c]The reaction was performed from −10 to 25 °C. [d]The reaction was carried out at 60 °C. [e]1.5 equiv of **2a** was used. [f]2.0 equiv of **1a**, 1.5 equiv of **3a**, and 4.0 equiv of KF/18-crown-6 were used.

formed in reduced yield when the reaction was performed in DME (entry 2). The use of other fluoride sources such as CsF and tetrabutyl ammonium fluoride (TBAF) provided only traces of the desired product (entries 3, 4). The optimal reaction temperature was found to be 25 °C as the reactions performed at lower and higher temperature afforded a lower yield of **4a** and a better yield of **5a** (entries 5, 6). Interestingly, when the reaction was performed using 1.5 equiv of **3a**, the target product **4a** was formed in 51% yield with high selectivity (entry 7). Performing the reaction with 2.0 equiv of **1a** and 1.5 equiv of **3a** improved the yield of **4a** to 72% while maintaining high selectivity (entry 8). This set of conditions was chosen for the substrate scope analysis.[20]

With the favorable reaction conditions in hand, we then studied the substrate scope of this three-component coupling. First, we evaluated the variation on aromatic tertiary amines (Scheme 2). Several *N,N*-dimethyl anilines bearing electron-releasing, -neutral and -withdrawing groups at the 4-position of the aromatic ring were well tolerated under these conditions resulting in the formation of the 2-selanyl aniline derivatives in moderate to good yields (**4a**−**4i**). In the case of the 4-bromo-*N,N*-dimethylaniline derived *o*-selanyl aniline derivative **4f**, the structure was confirmed by single crystal X-ray analysis (CCDC 1953258). Notably, the use of diphenyl diselenide as the electrophilic selenium source provided comparable results (**4a**, **4b**, **4c**, **4f**). Moreover, reactions carried out using an aromatic tertiary amine having a substituent at the 3-position, 2-position as well as disubstitution resulted in the formation of the desired products in moderate to good yields (**4j**−**4p**). It is noteworthy that a tertiary amine with an *α,β*-unsaturated ester moiety furnished the product **4q** in 50% yield.

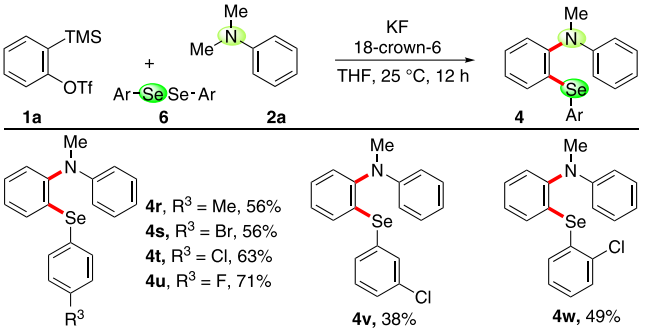
Next, we examined the scope of electrophilic selenium source in this reaction (Scheme 3). The substituted diaryl diselenides were used as the selenium source due to their ease of preparation. Differently substituted diaryl diselenides having a substituent at the 4-position of the ring are well tolerated, and the corresponding products are formed in good yields

**Scheme 2. Substrate Scope of Aromatic Tertiary Amines**[a]




[a]General conditions: **1a** (1.0 mmol), **2** (0.5 mmol), **3a** (0.75 mmol), KF (4.0 equiv), 18-crown-6 (4.0 equiv), THF (2.0 mL), 25 °C and 12 h. Yields of isolated products are given. [b]Diphenyl diselenide was used as the Se source. [c]Reaction was run on a 0.25 mmol scale of **2**. [d]Reaction was performed at 65 °C for 12 h. [e]$^1$H NMR yield of the product is provided.

**Scheme 3. Substrate Scope of Selenium Source**[a]




[a]General conditions: **1a** (0.5 mmol), **6** (0.375 mmol), **2a** (0.25 mmol), KF (4.0 equiv), 18-crown-6 (4.0 equiv), THF (1.0 mL), 25 °C and 12 h. Yields of isolated products are given.

(**4r**−**4u**). Moreover, diselenide having chlorine at the 3- and 2-position of the aromatic ring also afforded the aminoselenated products in moderate yields (**4v**, **4w**). Notably, the insertion of an aryne to the Se−Se bond of **6** was not observed probably due to the nucleophilicity of the tertiary amines.[15]

The tolerance of substituents on the aryne moiety was also studied (Table 2). 2-Selanyl aniline derivatives **4x**−**4z** are formed in moderate to good yields when this three-component reaction was performed using electronically dissimilar 4,5-disubstituted symmetrical arynes generated from the precursors (**1b**−**d**). Moreover, the unsymmetrical naphthalyne and tetrahydronaphthalyne generated from precursors **1e** and **1f** were well tolerated to furnish the single regioisomers **4aa** and **4ab** in 48% and 68% yield, respectively.[21] In addition, the unsymmetrical 4-methyl aryne formed from **1g** afforded an inseparable mixture of regioisomers **4ac** and **4ac′** in 74% yield and a 1.4:1 regioisomer ratio. Similarly, inseparable regioisomeric products were formed when the reaction was carried out using unsymmetrical 4-chloro and 4-fluoro arynes.



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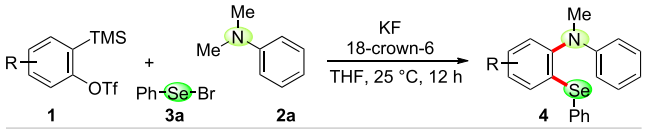
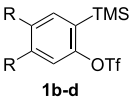
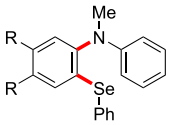
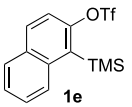
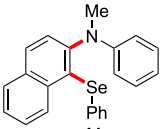
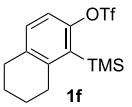
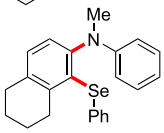
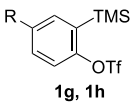
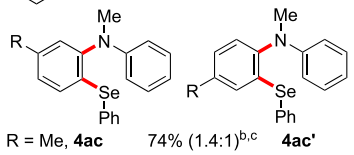
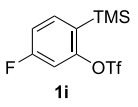
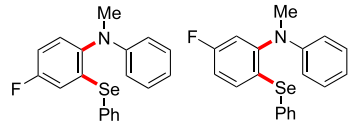
**Table 2. Variation of the Aryne Moiety**[a]



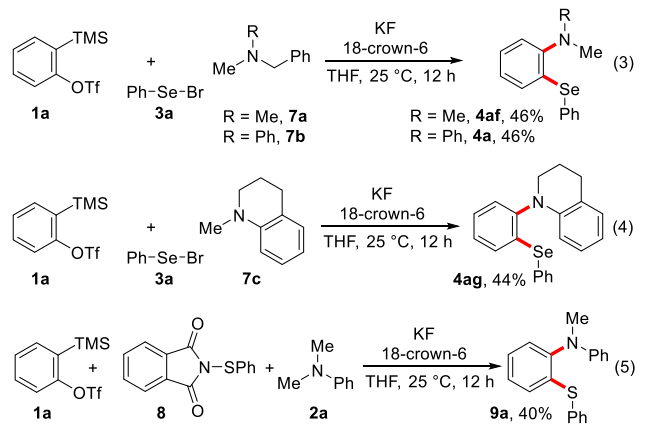

1 3a 2a 4

| entry | aryne precursor | product(s), yield (%) |
|---|---|---|
| 1<br>2<br>3 |  1b-d |  **4x**, R = Me, 68%<br>**4y**, R = $(CH_2)_3$, 79%<br>**4z**, R = F, 55% |
| 4 |  1e |  **4aa**, 48%[b] |
| 5 |  1f |  **4ab**, 68% |
| 6<br>7 |  1g, 1h |  R = Me, **4ac** 74% (1.4:1)[b,c] **4ac'**<br>R = Cl, **4ad** 68% (1.7:1)[c] **4ad'** |
| 8 |  1i |  **4ae** 56% (2.3:1)[c] **4ae'** |

[a]General conditions: **1** (1.0 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), KF (4.0 equiv), 18-crown-6 (4.0 equiv), THF (2.0 mL), 25 °C and 12 h. Yields of isolated products are given. [b]Reaction was performed on 0.25 mmol scale of **2a**. [c]Regioisomer ratio was determined by $^1$H NMR analysis.

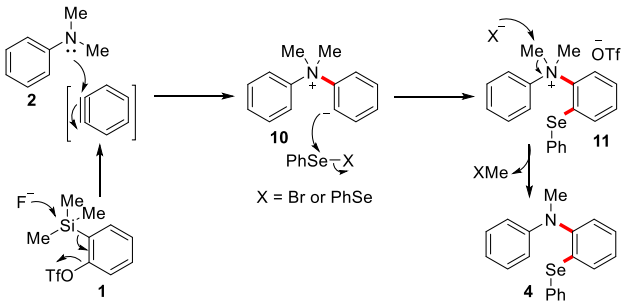
Interestingly, when the present three-component reaction was carried out using an aliphatic tertiary amine **7a**, the aminoselenated product **4af** was formed in 46% yield via a selective debenzylation instead of a demethylation (Scheme 4, eq 3). A similar reaction course via the debenzylation was observed when the reaction was performed using *N*-benzyl-*N*-methyl aniline **7b**, and the product **4a** was formed in 46% yield. In both cases, considerable amounts of tertiary amine were unreacted, which explains the moderate yield of products formed. Moreover, the reaction of aryne generated from **1a** and **3a** with *N*-methyl tetrahydroquinoline **7c** under the present conditions afforded the aminoselenated product **4ag** in 44% yield with 32% recovery of **7c** (eq 4). Furthermore, the present three-component reaction is not limited to amino-selenation, but the method can be extended to aminothiolation using **8** as the thiolating reagent and the corresponding product **9a** was formed in 40% yield (eq 5).[22]

**Scheme 4. Aminoselenation and Aminothiolation of Arynes**



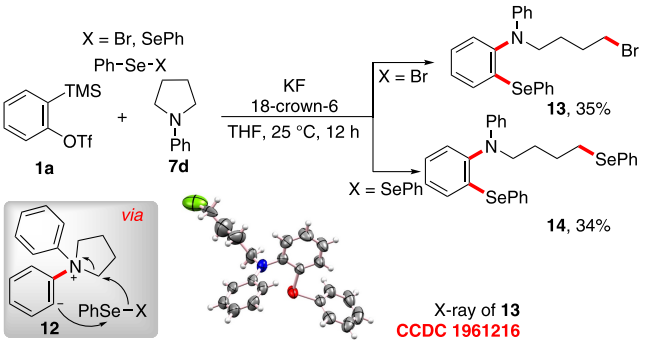

Mechanistically, the reaction proceeds via the nucleophilic addition of tertiary amine **2** to the in situ generated aryne (formed by the fluoride induced 1,2-elimination from **1**) resulting in the formation of the 1,3-zwitterionic intermediate **10** (Scheme 5). This aryl anion intermediate adds to the electrophilic selenium source to form the ammonium salt **11**. The rapid demethylation of the salt **11** most likely by the nucleophile $X^-$ results in the formation of the desired product **4**.

**Scheme 5. Proposed Mechanism of the Reaction**




Direct evidence for the suggested mechanism and the role of the nucleophile in the dealkylation step was obtained when the three-component reaction was performed using *N*-phenyl pyrrolidine **7d**. Treatment of the triflate **1a** with bromide **3a** and amine **7d** under the optimized conditions resulted in the formation of the product **13** in 35% yield (Scheme 6). The structure of **13** was confirmed by single crystal X-ray analysis (CCDC 1961216). A similar result was obtained using **6a** as the selenium source, and the corresponding product **14** was formed in 34% yield.[23] The initially formed 1,3-zwitterionic intermediate **12** from **7d** and aryne could add to the selenium source, and the eliminated $X^-$ could open the cyclic quaternary ammonium salt to form the desired products **13** and **14**.

**Scheme 6. Reaction Using Cyclic Tertiary Amine**




In conclusion, we have developed the three-component coupling of arynes, tertiary amines, and electrophilic selenium reagents for the synthesis of 2-selanyl aniline derivatives in



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moderate to good yields. This aminoselenation of arynes took place under mild and operationally simple conditions with the formation of a C−N and C−Se bond. Mechanistic studies clearly show the role of the leaving group on the selenium reagent, which acts as a nucleophile for the dealkylation leading to the final product. Further studies on related aryne three-component coupling reactions are ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03789.

Details on experimental procedures, characterization, and NMR spectra of functionalized 2-selanyl aniline derivatives (PDF)

### Accession Codes

CCDC 1953258 and 1961216 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(23) The product derived from the insertion of aryne to a Se−Se bond was obtained in 19% yield. For more details, see ref 15.



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