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Yuyao Shi, Pingfan Li

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Transition-metal-free Phenylselenylation of Arenes with Triflic Anhydride Activated Methyl Phenyl Selenoxide

Yuyao Shi and Pingfan Li*

Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology,

Beijing 100029, China

*E-mail: lipf@mail.buct.edu.cn

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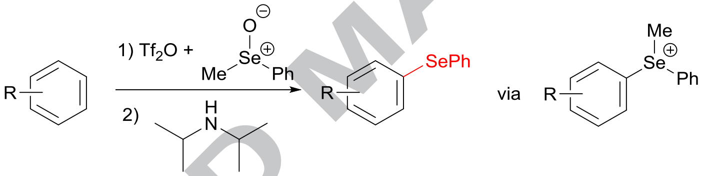

Phenylselenylation of arenes were achieved in a one-pot procedure by treating arene substrates with triflic anhydride activated methyl phenyl selenoxide, and then demethylation with diisopropylamine. This reaction provide a convenient method to prepare diarylselenide products under transition-metal-free conditions.

Organoselenides, in particular diarylselenides,[1] are a class of molecules with important biological activity.[2] Traditional methods for the synthesis of diarylselenides usually involves the reaction between aryl Grignard or aryllithium reagents with electrophilic arylselenium reagents,[3] or alternatively, aryldiazonium salts with nucleophilic arylselenium reagents.[4] Transition-metal catalyzed cross-coupling reactions between aryl halides or aryl boronic acids with phenylselenyl chloride, diphenyl diselenide or phenylselenyl tributyltin reagents were also extensively examined.[5] Recently, a number of transition-metals have been used to catalyzed the phenylselenylation of arene C-H bonds ortho to the directing groups, including palladium,[6] rhodium,[7] ruthenium,[8] copper,[9] and iron (Scheme 1a).[10] For the synthesis of α,β-unsaturated carbonyl compounds through oxidation and elimination of corresponding α-selenylated carbonyl compounds, phenylselenylation of enol derivatives were widely used to prepare such precursors.[11] Phenylselenylation of alkenes were also accomplished with electrophilic arylselenium reagents, and there has been some great interest to render such reactions catalytic enantioselective.[12] However, if phenylselenylation of arenes were attempted with PhSeCl, except for electron-rich aniline type substrates, chlorination products were obtained in most cases instead of the desired selenylation products (Scheme 1b).[13]

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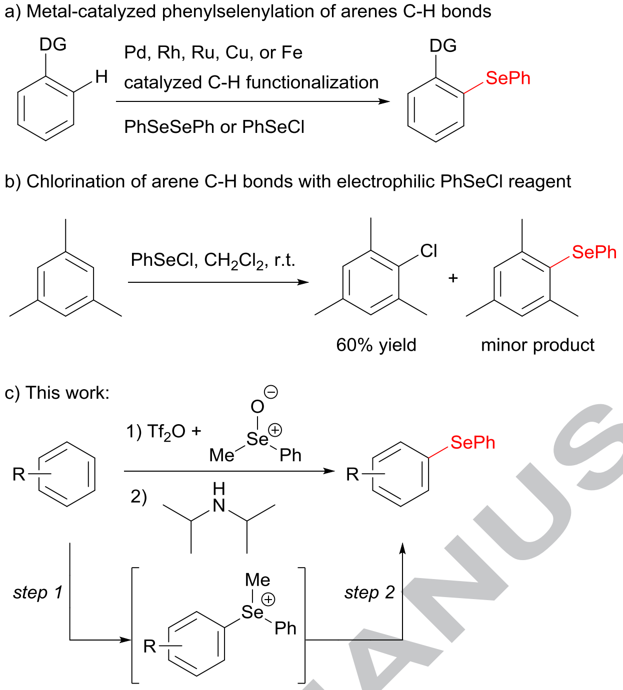
Scheme 1. Phenylselenylation of arene C-H bonds. DG = directing groups, Tf_2O = trifluoromethanesulfonic anhydride



In connection with our group's continuous interest in sulfur mediated C-H functionalization reactions,[14] and Procter's report for the synthesis of diarylthioethers through triflic anhydride activated sulfoxides,[15] we would like to extend such reactions to the corresponding selenium versions. It should be noted that despite the recent interest in studying various reactivity of triflic anhydride activated sulfoxides,[16] research work on corresponding selenium version is still very rare. We report herein our results for the preparation diarylselenides under transition-metal-free conditions through a one-pot, two-step sequence: electrophilic substitution of arenes with triflic anhydride activated methyl phenyl selenoxide, and then demethylation of the initially formed diaryl methyl selenonium salt with diisopropylamine (Scheme 1c).

The reaction between *p*-xylene (**1a**) and triflic anhydride activated methyl phenyl selenoxide (**2**) was chosen as the model reaction to optimize the reaction conditions (Scheme 2). When 2.1 equivalent of DBU was used as the base for the demethylation step, the desired product **3a** was isolated in 13% yield (entry 1). The use of pyridine type bases did not improve the reaction yield (entries 2-5), while MeONa/MeOH gave 31% yield (entry 6). We then screened a number of amine bases (entries 7-12), and the best result was obtained with diisopropylamine (entry 12). By increasing the amount of diisopropylamine, up to 87% yield of **3a** was obtained (entries 13-15). Increasing the reaction time for the second step did not increase the isolated yield (compare entries 14 and16), while the yield dropped at higher temperature (entry 17). Finally, 92% yield of **3a** was obtained when we lowered the reaction temperature for the second step to 0 °C (entry 18). Thus, the optimized one-pot, two-step reaction procedure was: dissolve **2** with CH_2Cl_2, add Tf_2O at −35 °C, and then add **1a**. After 15 min, the reaction tube was warmed up to room temperature for 1.5 h. After cooling down to 0 °C, diisopropylamine was added and stirred for 11 h before quenching.

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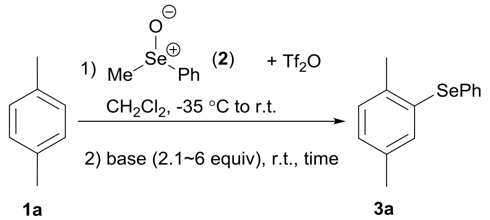
Scheme 2. Optimization of reaction conditions



entry	base	equiv	time (h)	yield (%)[a]
1	DBU	2.1	4	13
2	pyridine	2.1	4	10
3	2,6-lutidine	2.1	4	trace
4	2,6-dichloropyridine	2.1	4	10
5	2,6-difluoropyridine	2.1	4	trace
6	MeONa/MeOH	2.1	4	31
7	Et_2NH	2.1	4	5
8	Et_3N	2.1	4	15
9	morpholine	2.1	4	8
10	$^nPr_2NH$	2.1	4	23
11	$^tBuNH_2$	2.1	4	15
12	$^iPr_2NH$	2.1	4	31
13	$^iPr_2NH$	4.2	4	54
14	$^iPr_2NH$	5	4	87
15	$^iPr_2NH$	6	4	79
16	$^iPr_2NH$	5	11	87
17	$^iPr_2NH$	5	11	48[b]
18	$^iPr_2NH$	5	11	92[c]

[a] Isolated yields after flash column chromatography. [b] The second step was conducted at 40 °C. [d] The second step was conducted at 0 °C.

We then explored the substrate scope for a number of arene substrates to synthesize corresponding diarylselenide products (Scheme 3). As expected for the electrophilic substitution reaction during the first step that lead to diaryl methyl selenonium salt, electron-rich arene substrates generally react better for this reaction. *p*-Xylene (**1a**) and *m*-xylene (**1b**) gave **3a** and **3b** in 92% and 94% yield, respectively. Mesitylene (**1c**) gave product **3c** in a slightly lower 85% yield, probably because the arene substrate **1c** is sterically more hindered than **1a** and **1b**. 1,4-dimethoxybenzene (**1d**), 1,3,5-trimethoxybenzene (**1e**) and 1,2,3-trimethoxybenzene (**1f**) gave products **3d**, **3e** and **3f** in 82%, 87% and 83% yield, respectively. 2-Iodoanisole (**1g**) and 3-iodoanisole (**1h**) gave **3g** and **3h** in 74% and 69% yield, respectively. Product **3i** bearing a bromo substituent can also be prepared in 64% yield. 2-methoxynaphthalene (**1j**) gave product **3j** in 77% yield. Less electron-rich biphenyl (**1k**) reacted poorly, and the desired product **3k** was isolated in only 22% yield. For heteroarene substrates, thiophene (**1l**) also gave corresponding diarylselenide **3l** in 86% yield. All these products were obtained without abnormal regioselectivity issues. Other arene substrates (data not shown in scheme 3), such as benzene, toluene, halobenzenes, and naphthalene, all gave less than 10% yield and mixture of regioisomers. Arenes containing electron-withdrawing groups, such as carbonyl groups, were not reactive under these conditions. On the other hand, electron-rich heteroarenes, such as furan and indole, gave complex mixture and no major products were isolated.

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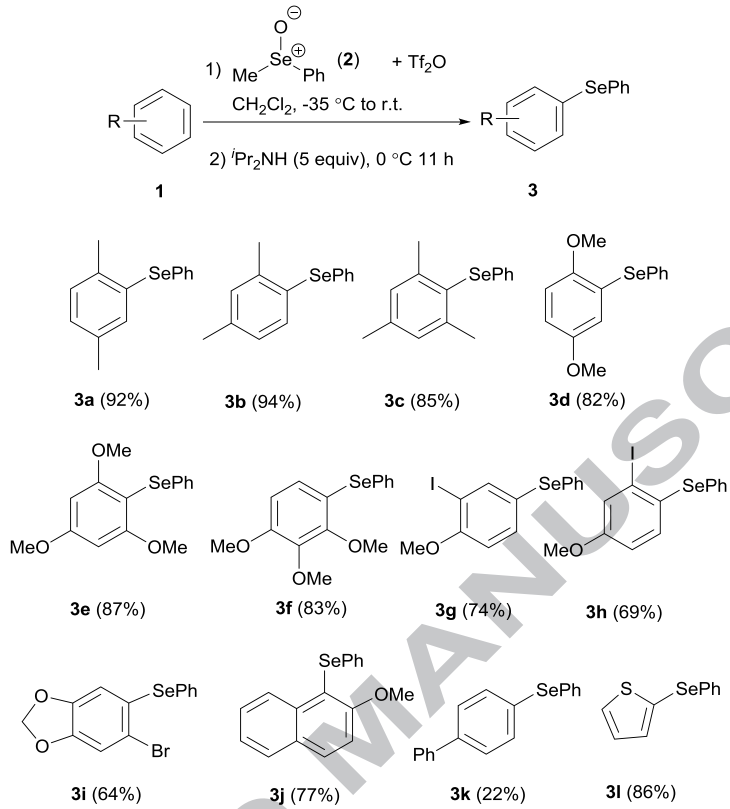
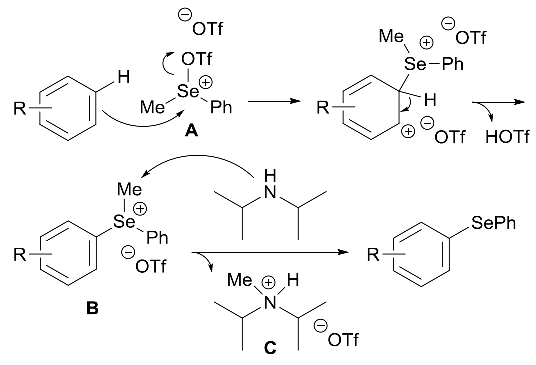
Scheme 3. Substrate scope



The proposed reaction mechanism is shown in Scheme 4. Oxyselenonium salt **A** generated from selenoxide and triflic anhydride was attacked by electron-rich arene substrates to give the electrophilic aromatic substitution products **B** as key intermediates after step 1, whose methyl group was attacked by the nucleophilic amine nitrogen to give the desired phenylselenylation products and ammonium salt **C** as by-product.

Scheme 4. Proposed mechanism



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In summary, we developed a convenient method for the preparation of diarylselenides through phenylselenylation of arenes in a one-pot procedure by treating arene substrates with triflic anhydride activated methyl phenyl selenoxide, and then demethylation with diisopropylamine. We are currently exploring other synthetic applications of such highly electrophilic selenium reagent generated from selenoxide and triflic anhydride, and those results will be reported in due course.

Acknowledge

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Notes and references

1. (a) Woods, J. A.; Hadfield, J. A.; McGown, A. T.; Fox, B. W., Bioactivity and molecular modelling of diphenylsulfides and diphenylselenides. *Bioorg. Med. Chem.* **1993,** *1* (5), 333-340; (b) Engman, L.; Stern, D.; Frisell, H.; Vessman, K.; Berglund, M.; Ek, B.; Andersson, C.-M., Synthesis, antioxidant properties, biological activity and molecular modelling of a series of chalcogen analogues of the 5-lipoxygenase inhibitor DuP 654. *Bioorg. Med. Chem.* **1995,** *3* (9), 1255-1262.

2. Mugesh, G.; du Mont, W.-W.; Sies, H., Chemistry of Biologically Important Synthetic Organoselenium Compounds. *Chem. Rev.* **2001,** *101* (7), 2125-2180.

3. (a) Campbell, T. W.; McCullough, J. D., The Synthesis of Unsymmetrical Selenides. *J. Am. Chem. Soc.* **1945,** *67* (11), 1965-1966; (b) Greenberg, B.; Gould, E. S.; Burlant, W., The Reaction of Aryllithium Compounds with Aryl Selenocyanates. A New Synthesis of Unsymmetric Diaryl Selenides1. *J. Am. Chem. Soc.* **1956,** *78* (16), 4028-4029.

4. Evers, M. J.; Christiaens, L. E.; Renson, M. J., Aryl arylazo sulfones chemistry. 2. Reactivity toward

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

alkaline alkane- and arene selenolate and alkane- and arenetellurolate anions. *J. Org. Chem.* **1986,** *51* (26), 5196-5198.

5. (a) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V., New approaches to the synthesis of unsymmetrical diaryl selenides. *J. Organomet. Chem.* **2000,** *605* (1), 96-101; (b) Kumar, S.; Engman, L., Microwave-Assisted Copper-Catalyzed Preparation of Diaryl Chalcogenides. *J. Org. Chem.* **2006,** *71* (14), 5400-5403; (c) Zhao, H.; Hao, W.; Xi, Z.; Cai, M., Palladium-catalyzed cross-coupling of PhSeSnBu3 with aryl and alkyl halides in ionic liquids: a practical synthetic method of diorganyl selenides. *New J. Chem.* **2011,** *35* (11), 2661-2665; (d) Zheng, B.; Gong, Y.; Xu, H.-J., Copper-catalyzed C–Se coupling of diphenyl diselenide with arylboronic acids at room temperature. *Tetrahedron* **2013,** *69* (26), 5342-5347; (e) Kumar, A.; Kumar, S., A convenient and efficient copper-catalyzed synthesis of unsymmetrical and symmetrical diaryl chalcogenides from arylboronic acids in ethanol at room temperature. *Tetrahedron* **2014,** *70* (9), 1763-1772.

6. (a) Iwasaki, M.; Tsuchiya, Y.; Nakajima, K.; Nishihara, Y., Chelate-Assisted Direct Selenation of Aryl C–H Bonds with Diselenides Catalyzed by Palladium. *Org. Lett.* **2014,** *16* (18), 4920-4923; (b) Iwasaki, M.; Kaneshika, W.; Tsuchiya, Y.; Nakajima, K.; Nishihara, Y., Palladium-Catalyzed peri-Selective Chalcogenation of Naphthylamines with Diaryl Disulfides and Diselenides via C–H Bond Cleavage. *J. Org. Chem.* **2014,** *79* (23), 11330-11338; (c) Jin, W.; Zheng, P.; Wong, W.-T.; Law, G.-L., Efficient Palladium-Catalyzed Direct C−H Phenylselenylation of (Hetero)Arenes in Water. *Asian J. Org. Chem.* **2015,** *4* (9), 875-878; (d) Vásquez-Céspedes, S.; Ferry, A.; Candish, L.; Glorius, F., Heterogeneously Catalyzed Direct C・H Thiolation of Heteroarenes. *Angew.*

ACCEPTED MANUSCRIPT

Chem. Int. Ed. **2015,** *54* (19), 5772-5776; (e) Jin, W.; Zheng, P.; Law, G.-L.; Wong, W.-T., Palladium(II)-catalyzed switchable mono-/diselenylation of arenes controlled by solvent effects. *J. Organomet. Chem.* **2016,** *812*, 66-73; (f) Qiu, R.; Reddy, V. P.; Iwasaki, T.; Kambe, N., The Palladium-Catalyzed Intermolecular C–H Chalcogenation of Arenes. *J. Org. Chem.* **2015,** *80* (1), 367-374.

7. (a) Yu, S.; Wan, B.; Li, X., Rh(III)-Catalyzed Selenylation of Arenes with Selenenyl Chlorides/Diselenides via C–H Activation. *Org. Lett.* **2015,** *17* (1), 58-61; (b) Xie, W.; Li, B.; Wang, B., Rh(III)-Catalyzed C7-Thiolation and Selenation of Indolines. *J. Org. Chem.* **2016,** *81* (2), 396-403.

8. (a) Shu, S.; Fan, Z.; Yao, Q.; Zhang, A., Ru(II)-Catalyzed Direct C(sp2)–H Activation/Selenylation of Arenes with Selenyl Chlorides. *J. Org. Chem.* **2016,** *81* (13), 5263-5269; (b) Mandal, A.; Dana, S.; Sahoo, H.; Grandhi, G. S.; Baidya, M., Ruthenium(II)-Catalyzed ortho-C–H Chalcogenation of Benzoic Acids via Weak O-Coordination: Synthesis of Chalcogenoxanthones. *Org. Lett.* **2017,** *19* (9), 2430-2433.

9. Mandal, A.; Sahoo, H.; Baidya, M., Copper-Catalyzed 8-Aminoquinoline-Directed Selenylation of Arene and Heteroarene C–H Bonds. *Org. Lett.* **2016,** *18* (13), 3202-3205.

10. Zhang, M.; Zhang, S.; Pan, C.; Chen, F., Iron-Catalyzed Direct C-H Thiolation of Trimethoxybenzene with Disulfides. *Synth. Commun.* **2012,** *42* (19), 2844-2853.

11. Reich, H. J.; Wollowitz, S., Preparation of α,β-Unsaturated Carbonyl Compounds and Nitriles by Selenoxide Elimination. In *Organic Reactions*, John Wiley & Sons, Inc.: 2004; Vol. 44:1, pp 1-296.

12. (a) Denmark, S. E.; Collins, W. R.; Cullen, M. D., Observation of Direct Sulfenium and Selenenium Group Transfer from Thiiranium and Seleniranium Ions to Alkenes. *J. Am. Chem. Soc.* **2009,** *131* (10),

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

3490-3492; (b) Kawamata, Y.; Hashimoto, T.; Maruoka, K., A Chiral Electrophilic Selenium Catalyst for Highly Enantioselective Oxidative Cyclization. *J. Am. Chem. Soc.* **2016,** *138* (16), 5206-5209.

13. (a) Ayorinde, F. O., PhSeCl as a chlorinating agent for activated benzene derivatives. *Tetrahedron Lett.* **1983,** *24* (20), 2077-2078; (b) Thurow, S.; Penteado, F.; Perin, G.; Jacob, R. G.; Alves, D.; Lenardao, E. J., Metal and base-free synthesis of arylselanyl anilines using glycerol as a solvent. *Green Chem.* **2014,** *16* (8), 3854-3859.

14. (a) Hu, G.; Xu, J.; Li, P., Sulfur Mediated Allylic C–H Alkylation of Tri- and Disubstituted Olefins. *Org. Lett.* **2014,** *16* (22), 6036-6039; (b) Zhang, Z.; Du, H.; Xu, J.; Li, P., Anti-Markovnikov rearrangement in sulfur mediated allylic C-H amination of olefins. *Chem. Commun.* **2016,** *52* (77), 11547-11550. (c) Li, X.; Li, P. *J. Beijing Univ. Chem. Technol. (Nat. Sci. Ed.)* **2017**, *44*(3), 8. (d) Hu, G.; Xu, J.; Li, P. *Org. Biomol. Chem.* **2018**, *16*, 4151-4158. (e) Hu, G.; Xu, J.; Li, P. *Org. Chem. Front.* **2018***,* DOI: 10.1039/C8QO00410B.

15. Fernandez-Salas, J. A.; Pulis, A. P.; Procter, D. J., Metal-free C-H thioarylation of arenes using sulfoxides: a direct, general diaryl sulfide synthesis. *Chem. Commun.* **2016,** *52* (83), 12364-12367.

16. (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J., Beyond the Pummerer Reaction: Recent Developments in Thionium Ion Chemistry. *Angew. Chem. Int. Ed.* **2010,** *49* (34), 5832-5844; (b) Pulis, A. P.; Procter, D. J., C−H Coupling Reactions Directed by Sulfoxides: Teaching an Old Functional Group New Tricks. *Angew. Chem. Int. Ed.* **2016,** *55* (34), 9842-9860; (c) Shafir, A., The emergence of sulfoxide and iodonio-based redox arylation as a synthetic tool. *Tetrahedron Lett.* **2016,** *57* (25), 2673-2682; (d) Yorimitsu, H., Cascades of Interrupted Pummerer Reaction-Sigmatropic Rearrangement. *Chem. Rec.* **2017**, *17*, 1156-1167; (e) Meng, L.; Zeng, J.; Wan, Q., Interrupted Pummerer Reaction in Latent/Active Glycosylation.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Synlett **2018,** *29* (2), 148-156; (f) Tian, Z.-Y.; Hu, Y.-T.; Teng, H.-B.; Zhang, C.-P., Application of arylsulfonium salts as arylation reagents. *Tetrahedron Lett.* **2018,** *59* (4), 299-309.

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Highlights

Highly electrophilic selenium reagent was generated from selenoxide and triflic anhydride.

The substitution reaction with such selenium reagent proceed with innate regioselectivity of the aromatic ring.

Demethylation of diaryl methyl selenonium salt is accomplished with diisopropylamine.

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