Organic LETTERS

Letter

pubs.acs.org/OrgLett

Chelate-Assisted Direct Selenation of Aryl C−H Bonds with Diselenides Catalyzed by Palladium

Masayuki Iwasaki,[†] Yuta Tsuchiya,[†] Kiyohiko Nakajima,[‡] and Yasushi Nishihara*[,†,§]

[†]Division of Earth, Life, and Molecular Sciences, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

[‡]Department of Chemistry, Aichi University of Education, Igaya, Kariya, Aichi 448-8542, Japan

[§]ACT-C, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

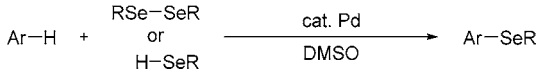
Supporting Information

ABSTRACT: A direct selenation of inert C−H bonds of benzamide derivatives and their related compounds with diselenides has been achieved with the palladium catalyst. The reaction was compatible with a variety of functional groups, including a bromo group. Primitive mechanistic insights revealed that the reaction proceeded through a C−H bond cleavage and the sequential oxidative addition of diselenides. The present synthetic method can be applied to the facile synthesis of selenoxanthone which can be regarded as promising heterocyclic materials.

Organoselenium compounds play an important role in organic synthesis because of their potential biological activities.[1] Among these compounds, aryl selenide scaffolds are often found in drug candidates and bioactive compounds.[2] Moreover, they also have significant applications to functional organic materials.[3] The preparation of aryl selenides has therefore attracted considerable interest since early times. Although a large number of synthetic methods of aryl selenides have been developed, transition-metal-catalyzed C−Se bond formation represents a powerful and reliable procedure.[4] Most methods reported are mainly divided into (a) electrophilic selenation and (b) nucleophilic selenation. The former is the electrophilic substitution of arylmetal reagents with selenium electrophiles,[5] while the latter is the reaction of aryl halides with diselenides,[6] $RSeSnR'_3$,[7] and other nucleophiles.[8,9] Those methods provide the target aryl selenides efficiently, but the starting aryl substrates have to be prefunctionalized, which is a significant drawback. To overcome the problems, several efficient catalytic systems have been well developed for the formation of carbon−heteroatom (B, N, O, Si, P, Sn, Ge, halogen, etc.) bonds via a C−H bond cleavage.[10] However, a direct selenation of an inert aryl C−H bond had not been disclosed to date due to the strong coordinating property of the organoselenium compounds,[11] while Friedel−Crafts selenation of electron-rich arenes and heteroarenes has been known.[12]

Recently, we[13] and other groups[14] independently developed the catalytic C−H thiolation of arenes bearing directing groups. Herein, we report the first direct selenation of aryl C−H bonds with diselenides or selenols by a simple palladium catalyst, which provides a new entry to the synthesis for aryl selenides (Scheme 1). The key to its success is an introduction of appropriate directing groups, which could suppress deactivation and/or aggregation of the catalyst.

Scheme 1. Direct Selenation of Aryl C−H Bonds

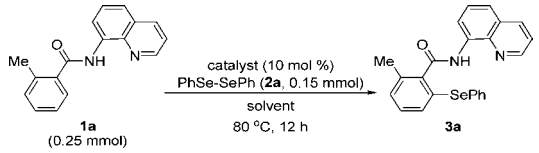


Since Daugulis' pioneering work,[15] 8-aminoquinolinamide and picolinamide can be utilized as efficient and promising bidentate directing groups for a direct functionalization of C−H bonds.[16] Inspired by this knowledge, we initially investigated the direct selenation of benzamide derivative **1a** (0.25 mmol) with diphenyl diselenide (**2a**, 0.15 mmol) in DMSO (0.7 mL) at 80 °C for 12 h (Table 1). The selenated product **3a** was not observed without any catalyst (entry 1). We also confirmed that $Cu(OAc)_2$[14a] and $[Cp^*RhCl_2]_2$[14b] showed no catalytic activity in this reaction although those complexes can mediate or catalyze the direct thiolation reaction (entries 2 and 3). To our delight, the desired product **3a** was obtained in 85% yield when 10 mol % of $PdCl_2(NCPh)_2$ was used as the catalyst (entry 4). As far as we tested, DMSO was found to be the optimal solvent, which would also act as the terminal oxidant. Other solvents such as DMF (11%), toluene (5%), and ᵗPentOMe (6%) diminished the yields (entries 5−7). After several surveys of other palladium precursors, we found that $Pd(OAc)_2$, a commonly used catalyst in direct functionalization, was less reactive (entry 8). Employment of palladium(0) complexes, $Pd(PPh_3)_4$ and $Pd(dba)_2$, decreased the product yields (entries 9 and 10). The amounts of $PdCl_2(NCPh)_2$ and **2a** can be reduced to 5 mol % and 0.125 mmol, respectively, thus affording **3a** in 95% yield (entry 11). It is worth noting that only 2.5 mol % of $PdCl_2(NCPh)_2$ functioned to catalyze the reaction (entry 12). The selenated product **3a** was isolated and

Received: August 17, 2014
Published: September 10, 2014

dx.doi.org/10.1021/ol502439m | Org. Lett. 2014, 16, 4920−4923

Table 1. Palladium-Catalyzed Direct Selenation of Benzamides Derivatives 1a with Diphenyl Diselenide (2a)



			yield (%)[a]	
entry	catalyst	solvent	3a	1a
1	none	DMSO	0	98
2	$Cu(OAc)_2$	DMSO	12	78
3	$[Cp^*RhCl_2]_2$	DMSO	0	98
4	$PdCl_2(NCPh)_2$	DMSO	85	13
5	$PdCl_2(NCPh)_2$	DMF	11	80
6	$PdCl_2(NCPh)_2$	toluene	5	74
7	$PdCl_2(NCPh)_2$	^{t}PentOMe	6	76
8	$Pd(OAc)_2$	DMSO	37	56
9	$Pd(PPh_3)_4$	DMSO	16	68
10	$Pd(dba)_2$	DMSO	37	51
11[b,c]	$PdCl_2(NCPh)_2$	DMSO	95 (90)	0
12[c,d]	$PdCl_2(NCPh)_2$	DMSO	91	5

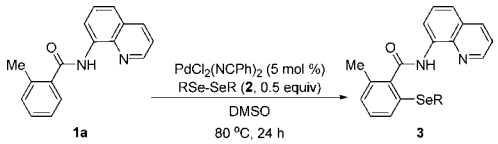
[a]Yields were determined by NMR. An isolated yield is shown in parenthesis. [b]$PdCl_2(NCPh)_2$ (5 mol %) was used. [c]PhSe−SePh (0.125 mmol) was used, and the reaction was performed for 24 h. [d]$PdCl_2(NCPh)_2$ (2.5 mol %) was used.

fully characterized by NMR spectroscopies, and the structure was further confirmed by X-ray diffraction analysis.[17]

Neither *N*-methyl nor benzoyl analogue of **1a** underwent the reaction with **2a** under the optimized conditions.[18] The anionic and neutral *N*,*N*-bidentate chelation nature of an *N*-(8-quinolyl)amide moiety in **1a** was found to be critical in this transformation.[16]

With the optimized conditions in hand, we then conducted the direct selenation of **1a** with an array of diselenides **2**, and the results are summarized in Table 2. In addition to diphenyl diselenide (**2a**), electron-rich methoxy-substituted diaryl diselenide **2b** participated in the reaction (entry 2). Moreover, bromo and chloro groups were totally tolerated under identical conditions (entries 3 and 4). Interestingly, the corresponding selenated products **3c** and **3d** were obtained in good yields,

Table 2. Diselenide Scope in Direct Selenation of Benzamide 1a



entry	R (2)	product	yield (%)[a]
1	Ph (**2a**)	**3a**	90
2	*p*-$MeOC_6H_4$ (**2b**)	**3b**	89
3	*p*-BrC_6H_4 (**2c**)	**3c**	82
4	*p*-ClC_6H_4 (**2d**)	**3d**	87
5	*o*-MeC_6H_4 (**2e**)	**3e**	75
6[b]	*o*-$CF_3C_6H_4$ (**2f**)	**3f**	98
7	2-thienyl (**2g**)	**3g**	70
8[b]	^{n}Bu (**2h**)	**3h**	62
9[b]	Me (**2i**)	**3i**	41

[a]Isolated yields. [b]RSe−SeR (1 equiv) was used.

while no arylated products were observed.[15,19] Diaryl diselenides **2e** and **2f** that bears electron diverse methyl and trifluoromethyl substituents at the *ortho* position also underwent the direct selenation of **1a** without any difficulties (entries 5 and 6). The feature of this synthetic method was further demonstrated by successful selenation with di(2-thienyl) diselenide, albeit in 70% yield (entry 7). Besides diaryl diselenide (**2g**), di(^{n}butyl)- (**2h**) and dimethyl diselenide (**2i**) were compatible with this protocol (entries 8 and 9). However, the direct telluration of **1a** with a corresponding diphenyl ditelluride did not proceed at this stage.

Subsequently, substitution effects in the benzamide were briefly evaluated (Figure 1). The introduction of a methyl group at the *meta* position gave only monoselenated product **3j** likely because of steric congestion which hampers further functionalization. In contrast, the reaction of a simple benzamide gave disubstituted product **3k** in 73% yield. Attempts to obtain a monoselenated product remained unsuccessful.

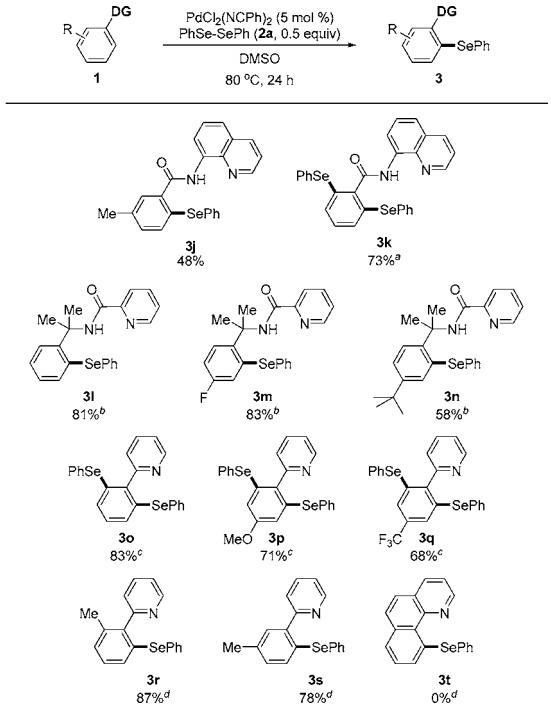


Figure 1. Substrate scope in direct selenation with **2a**: [a]PhSe−SePh (1.2 equiv). [b]120 °C. [c]$PdCl_2(NCPh)_2$ (10 mol %), PhSe−SePh (1.2 equiv), 140 °C, 12 h. [d]$PdCl_2(NCPh)_2$ (10 mol %), 120 °C, 12 h.

We also tested direct selenation of structurally related benzylamine derivatives with **2a**. The reaction efficiently proceeded to provide monoselenated product **3l** as we had expected. The results indicate that the repulsion between the sterically hindered directing group and the introduced seleno group would avoid the interaction of palladium with another C−H bond. Electronic properties on the benzene ring do not significantly affect the product yields (**3m** and **3n**).

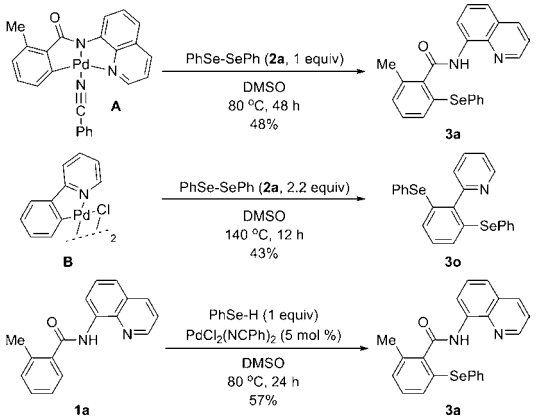
Various 2-arylpyridines were subjected to the direct selenation with **2a**. The reaction of 2-phenylpyridine proceeded well to yield the disubstituted product **3o** in 83% yield. Both electron-rich and -poor aryl C−H bonds were equally selenated (**3p** and **3q**). Notably, monoselenated products **3r** and **3s** were solely obtained when *ortho*- or *meta*-substituted 2-arylpyridines

dx.doi.org/10.1021/ol502439m | *Org. Lett.* 2014, 16, 4920−4923

were used. Benzoquinoline did not undergo the reaction probably due to the higher planarity that suppresses the C−H cleavage step.

The following control experiments provided some mechanistic insights (Scheme 2). A stoichiometric reaction of palladacycle **A**, prepared from **1a** and $Pd(OAc)_2$, with **2a** generated the desired product **3a** in 48% yield. Besides, the reaction of 2-phenylpyridine−palladium complex **B** with **2a** also proceeded to yield the target selenide **3o** in 43% yield. These experiments suggested that the palladacycle formed by C−H cleavage of arenes would be allowed to react with diselenide **2**, affording the selenated product **3**. The lower product yields in the stoichiometric reactions arise from the lower concentration of **2a**, compared to that of the palladium complexes. Therefore, an initial rate in the catalytic reaction could be faster, implying that this step may involve the rate-determining step. On the contrary, the reaction of the once isolated $[(Ph_3P)Pd(SePh)_2]_2$ (**C**) with **1a** gave no trace of **3a**. Additionally, the palladacycle **A** was found to successfully catalyze the reaction of **1a** with **2a** in the presence of 20 mol % of HCl ethereal solution to give **3a** in 70% yield. To our surprise, without HCl, **3a** was obtained in only 8% yield. These results imply that (1) complex **A** may be one of the intermediates or resting states in the present reaction and (2) the in situ formed HCl plays an important role in the catalytic reaction. In most cases, 0.5 equiv of diselenides **2** across **1** were enough to complete the reaction, which elucidates that both of the seleno moieties of **2** can be incorporated to the product **3**. We postulated that the generated selenols can be readily oxidized by DMSO to provide the diselenides, which is supported by the fact that the reaction of **1a** with benzeneselenol smoothly proceeded to yield **3a** in 57% yield under the optimized conditions.

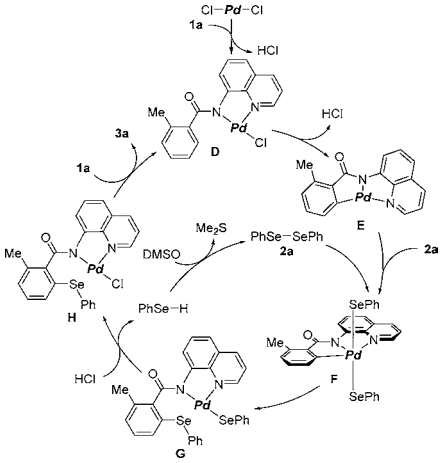
Scheme 2. Control Experiments



We then carried out several kinetic isotope experiments to better understand the reaction mechanism.[18] A significant primary kinetic isotope effect (KIE) was not observed for parallel experiments (k_H/k_D = 1.3) as well as intramolecular competition (k_H/k_D = 1.0). On the other hand, intermolecular competition provided a large KIE value (k_H/k_D = 3.2). These results indicated that the C−H bond cleavage in the present catalytic direct selenation would be not a rate-determining step but a product-determining one.[20]

On the basis of the above results and the literature information, although the present mechanistic consideration is premature, we are tempted to assume the reaction mechanism of **1a** with **2a** as shown in Scheme 3. An initial reaction of palladium dichloride with **1a** generates the palladium intermediate **D** ligated by the *N*,*N*-bidentate ligand. Subsequent C−H cleavage of **1a** gives the palladacycle **E**, similar to the complex **A** in Scheme 2, followed by oxidative addition of **2a** to form the high-valent palladium species **F**, being Pd(IV) or Pd(III).[10a,e,14c,21,22] The productive reductive elimination proceeds to afford **G** with C−Se bond formation. Neutralization of the palladium phenylselenide **G** with HCl affords the chloropalladium **H** and benzeneselenol, which would be an essential step for the catalytic reaction. The exact role of HCl remains to be elucidated, but in the absence of HCl, the palladium phenylselenide **G** could not cleave an aryl C−H bond due to the strong affinity of the Pd−Se bond. Simultaneously, the resulting selenol is oxidized by DMSO to regenerate **2a** quantitatively. Finally, ligand exchange of **H** with **1a** provides the product **3a** and regenerates the initial palladium **D**.

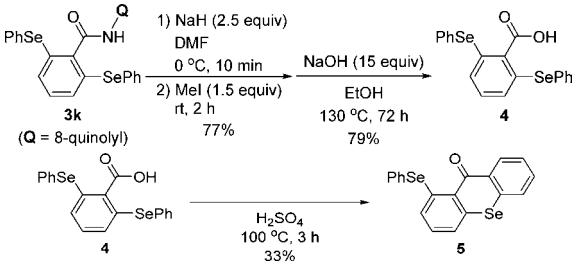
Scheme 3. Plausible Reaction Mechanism



The 8-quinolylamino group in **3a** can be readily removed according to Daugulis' report (Scheme 4). The protection of the NH moiety of **3a** with MeI, followed by hydrolysis with NaOH in EtOH, gave the corresponding benzoic acid **4** in good overall yield. The present direct selenation could be applied to the construction of selenoxanthone motifs, a key synthetic intermediate of selenoxanthylium dyes.[23] Intramolecular cyclization of **4** in sulfuric acid was successful to afford the desired product **5**.

In conclusion, we have developed the first palladium-catalyzed C−H selenation of benzamides, benzylamines, and 2-arylpyridines with the aid of the nitrogen-chelating groups. $PdCl_2(NCPh)_2$, a simple and readily available complex, can

Scheme 4. Removal of the 8-Aminoquinoline Auxiliary and Intramolecular Cyclization of 4



dx.doi.org/10.1021/ol502439m | Org. Lett. 2014, 16, 4920−4923

catalyze the direct selenation without any other metals or additives. The reaction provides the direct and atom-efficient synthetic method of aryl selenides under mild oxidative conditions. The directing group can be readily removed to afford the selenated benzoic acid which represents an important precursor of selenoxanthylium dyes. Efforts to expand the utility of this reaction and detailed mechanistic works by DFT calculation are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Details of all experiments procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ynishiha@okayama-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by a Grant-in-Aid for Scientific Research (KAKENHI) (No. 26810060) from JSPS and the Program for Promoting the Enhancement of Research Universities from MEXT and a Special Project of Okayama University. The authors gratefully thank Ms. Megumi Kosaka and Mr. Motonari Kobayashi at the Department of Instrumental Analysis, Advanced Science Research Center, Okayama University for measurement of elemental analyses and SC-NMR Laboratory of Okayama University for the NMR spectral measurement.

■ REFERENCES

(1) For recent reviews, see: (a) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255.

(2) (a) Woods, J. A.; Hadfield, J. A.; McGrown, A. T.; Fox, B. W. *Bioorg. Med. Chem.* **1993**, *1*, 333. (b) Engman, L.; Stern, D.; Frisell, H.; Vessman, K.; Berglund, M.; Ek, B.; Andersson, C.-M. *Bioorg. Med. Chem.* **1995**, *3*, 1255.

(3) (a) Okamoto, Y. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1986. (b) Ando, T.; Kwon, T. S.; Kitagawa, A.; Tanemura, T.; Kondo, S.; Kunisada, H.; Yuki, Y. *Macromol. Chem. Phys.* **1996**, *197*, 2803.

(4) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.

(5) (a) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241. (b) Ren, K.; Wang, M.; Wang, L. *Org. Biomol. Chem.* **2009**, *7*, 4858. (c) Ricordi, V. G.; Freitas, C. S.; Perin, G.; Lenardão, E. J.; Jacob, R. G.; Savegnago, L.; Alves, D. *Green Chem.* **2012**, *14*, 1030.

(6) (a) Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* **1999**, *1*, 1725. (b) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705. (c) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V.; Khrustalev, V. N. *Chem. Lett.* **2010**, *39*, 720. (d) Zhao, H.; Hao, W.; Xi, Z.; Cai, M. *New J. Chem.* **2011**, *35*, 2661.

(7) (a) Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915. (b) Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193. (c) Kumar, S.; Engman, L. *J. Org. Chem.* **2006**, *71*, 5400. (d) Fukuzawa, S.; Tanihara, D.; Kikuchi, S. *Synlett* **2006**, 2145. (e) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 951. (f) Chatterjee, T.; Ranu, B. C. *J. Org. Chem.* **2013**, *78*, 7145.

(8) (a) Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1981**, 151. (b) Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *Organometallics* **1985**, *4*, 657. (c) Evers, M. J.; Christiaens, L. E.; Renson, M. J. *J. Org. Chem.* **1986**, *51*, 5196. (d) Taniguchi, N. *Synlett* **2005**, 1687.

(9) Another type of the C−Se bond formation has been reported, see: Zhang, W.-X.; Wang, Z.; Xi, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 8122.

(10) For recent reviews on catalytic direct aryl C−X (B, N, O, Si, and halogen) bond formation, see: (a) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Vedernikov, A. N. *Acc. Chem. Res.* **2012**, *45*, 803. (e) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840. (f) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (g) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. For phosphonation, see: (h) Li, C.; Yano, T.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9801. For stannylation, see: (i) Doster, M. E.; Hatnean, J. A.; Jeftic, T.; Modi, S.; Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923. For germanylation, see: (j) Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968.

(11) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker: New York, 1984.

(12) (a) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732. (b) Shibahara, F.; Kanai, T.; Yamaguchi, E.; Kamei, A.; Yamauchi, T.; Murai, T. *Chem.—Asian J.* **2014**, *9*, 237.

(13) Iwasaki, M.; Iyanaga, M.; Tsuchiya, Y.; Nishimura, Y.; Li, W.; Li, Z.; Nishihara, Y. *Chem.—Eur. J.* **2014**, *20*, 2459.

(14) (a) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (b) Yang, Y.; Hou, W.; Qin, L.; Du, J.; Feng, H.; Zhou, B.; Li, Y. *Chem.—Eur. J.* **2014**, *20*, 416. (c) Xu, C.; Shen, Q. *Org. Lett.* **2014**, *16*, 2046.

(15) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(16) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726 and references therein.

(17) Crystallographic data for the structure of **3a** have been deposited with The Cambridge Crystallographic Data Centre as the deposition number CCDC-1019170. This data can be obtained free of charge from an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or www.ccdc.cam.ac.uk/data_request/cif.

(18) See the Supporting Information for details.

(19) For the palladium-catalyzed direct arylation of benzamides with aryl halides, see: (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (c) Shabashov, D.; Molina Maldonado, J. R.; Daugulis, O. *J. Org. Chem.* **2008**, *73*, 7818. (d) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380. (e) Péron, F.; Fossey, C.; Cailly, T.; Fabis, F. *Org. Lett.* **2012**, *14*, 1827. (f) Li, D.-D.; Yuan, T.-T.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 3341. (g) Misal Castro, L. C.; Chatani, N. *Chem.—Eur. J.* **2014**, *20*, 4548.

(20) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(21) Canty, A. J.; Jin, H.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1998**, *37*, 3975.

(22) The formation of the high-valent palladium species was not observed in ^{1}H NMR analyses, which would imply the fast reductive elimination to construct the C−Se bond.

(23) Brennan, N. K.; Donnelly, D. J.; Detty, M. R. *J. Org. Chem.* **2003**, *68*, 3344.