# Auto-Tandem Palladium Catalysis: From Isoxazole to 2-Azafluorenone

Sajal Das, Dongsub Hong, Zhiwei Chen, Zhigang She,[†] William H. Hersh, Gopal Subramaniam, and Yu Chen*

Department of Chemistry and Biochemistry, Queens College and the Graduate Center of the City University of New York, Flushing, New York 11367-1597, United States

S *Supporting Information*

ABSTRACT: An auto-tandem palladium catalysis from halogen-substituted isoxazoles and Michael acceptors is described. It involves two mechanistically distinct palladium-catalyzed reactions, a Heck reaction and a rearrangement, leading to 2-azafluorenones. It is the first example of palladium-catalyzed ring opening of isoxazoles and rearrangement of the β-imino ketone ring-opening product.
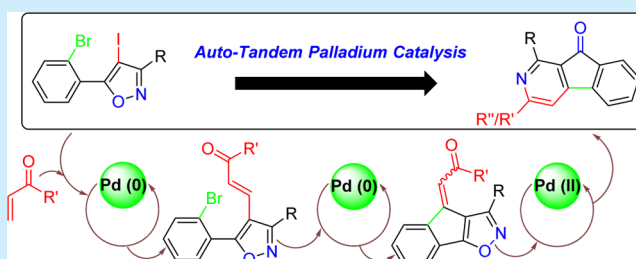
There has been growing interest in tandem catalysis because of the inherent features of these transformations,
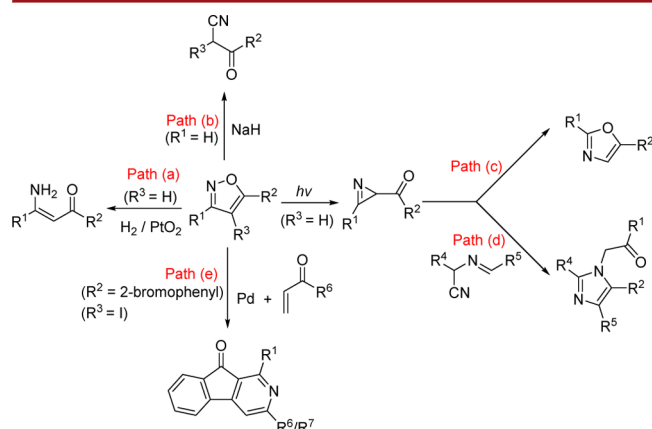

Figure 1. Isoxazoles as building blocks in organic synthesis.

such as atom economy, time and cost savings, environmental friendliness, and potential applications in the rapid construction of complex molecular structures.[1] Among the three categories of tandem catalytic transformations described by Fogg and dos Santos,[1a] auto-tandem catalysis is the most intriguing since one catalyst can promote two or more mechanistically distinct reactions in one reactor.[2] While auto-tandem catalysis has the intrinsic advantage of overall reaction efficiency, the development of new auto-tandem-catalyzed processes is still challenging because they are difficult to control and can be complicated by interference with side reactions, especially when the optimal conditions for multiple catalytic cycles differ from each other.

The prevalence of heterocycles in pharmaceuticals and functional materials has spurred the ongoing development of

Table 1. Tandem Palladium Catalysis: Optimization of the Reaction Conditions for 2-Azafluorenone Synthesis[a]

entry	catalyst (10 mol %)	base (2 equiv)	solvent	yield (%)[b]
1	Pd(PPh$_3$)$_4$	Li$_2$CO$_3$	NMP	27
2[c]	Pd(PPh$_3$)$_4$	Li$_2$CO$_3$	NMP	35
3[c,d]	Pd(PPh$_3$)$_4$	Li$_2$CO$_3$	NMP	0
4[c]	Pd(PPh$_3$)$_4$	Li$_2$CO$_3$	DMAc	34
5[c]	Pd(PPh$_3$)$_4$	Li$_2$CO$_3$	DMF	7
6[c]	PdCl$_2$(PPh$_3$)$_2$	Li$_2$CO$_3$	NMP	25
7[c]	Pd(OAc)$_2$ + 2PPh$_3$	Li$_2$CO$_3$	NMP	26
8[c]	PdCl$_2$ + 2PPh$_3$	Li$_2$CO$_3$	NMP	37
9[c]	PdBr$_2$ + 2PPh$_3$	Li$_2$CO$_3$	NMP	48
10[c]	PdBr$_2$ + BINAP	Li$_2$CO$_3$	NMP	57
11[c,e]	PdBr$_2$ + BINAP	Li$_2$CO$_3$	NMP	62
12[c,e]	PdBr$_2$ + BINAP	Na$_2$CO$_3$	NMP	39
13[c,e]	PdBr$_2$ + BINAP	K$_2$CO$_3$	NMP	13
14[c,e]	PdBr$_2$ + BINAP	Cs$_2$CO$_3$	NMP	0

[a]Conditions: **1a** (0.5 mmol), MVK (1.5 mmol), catalyst (10 mol %), base (2 equiv), 5 mL of solvent, 150 °C, 16 h, in a sealed 4 dram vial. [b]Isolated yields. [c]1 equiv of *n*-Bu$_4$NBr was added. [d]The reaction was carried out at 120 °C. [e]4 Å molecular sieves (80 wt % of **1a**) were added.

efficient synthetic protocols for heterocyclic compounds with high structural diversity and molecular complexity. 2-Azafluorenones are known as activating agents of phosphatidylinositol-

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Table 2. Tandem Palladium Catalysis: Scope of 2-Azafluorenone Synthesis[a]

entry	1	Michael acceptor	2 / yield[b]	entry	1	Michael acceptor	2 / yield[b]

(Reaction scheme: PdBr$_2$ (10 mol %), BINAP (10 mol %), Li$_2$CO$_3$ (2 equiv), n-Bu$_4$NBr (1 equiv), molecular sieves (4 Å), NMP, 150 °C, 16 h)

Entry 1: 1a (R^1 = t-Bu); Michael acceptor (vinyl ketone); products: R^3 = Me; 2a (62%); R^3 = Et; 2b (66%); R^3 = H; 2c (43%)

Entry 2: 1a; Michael acceptor; products 2d, 3d: R^3 = O-t-Bu: 2d (56%) + 3d (6%); R^3 = OMe: 2d (63%) + 3d (11%); R^3 = NMe$_2$: 2d (84%) + 3d (10%); R^3 = 4-morpholinyl: 2d (87%) + 3d (10%)

Entry 3[c]: R^1 = t-Bu; 1a, R^1 = i-Pr; 1f; Michael acceptor (acrylamide, N,N-dimethyl); products: R^1 = t-Bu; 2d (74%); R^1 = i-Pr; 2e (40%)

Entry 4: R^1 = t-Bu; 1a, R^1 = Ph; 1c; Michael acceptor (acrylonitrile, CN); products: R^1 = t-Bu; 2f (72%); R^1 = Ph; 2g (69%)

Entry 5[c]: R^1 = CMe$_2$Ph; 1b, R^1 = Ph; 1c; Michael acceptor (acryloyl morpholine); products: R^1 = CMe$_2$Ph; 2h (62%); R^1 = Ph; 2i; (89%)

Entry 6[c]: R^1 = Ph; 1d, R^1 = CMe$_2$Ph; 1e; Michael acceptor (acryloyl morpholine); products: R^1 = Ph; 2j (61%); R^1 = CMe$_2$Ph; 2k (71%)

Entry 7[c]: 1g (t-Bu, F); Michael acceptor (N,N-dimethyl acrylamide); product: 2l (62%)

Entry 8[c]: 1h (t-Bu, Me); Michael acceptor (N,N-dimethyl acrylamide); product: 2m (58%)

[a]Conditions: 1 (0.5 mmol), alkene (Michael acceptor) (1.5 mmol), PdBr$_2$ (10 mol %), BINAP (10 mol %), Li$_2$CO$_3$ (2 equiv), n-Bu$_4$NBr (1 equiv), 4 Å molecular sieves (80 wt % of 1), 5 mL of NMP, 150 °C, 16 h, in a sealed 4 dram vial. [b]Isolated yields. [c]The reaction was carried out in the absence of n-Bu$_4$NBr.

specific phospholipase C in C6 glioma cells.[3] Their unique chemical and biological characteristics have attracted the attention of synthetic organic chemists for decades. The known synthetic methods for 2-azafluorenones include (a) a three-component reaction protocol with Knoevenagel condensation as the key step,[4] (b) intramolecular acylation of 4-phenylpyridinyl substrates,[5] (c) a palladium-catalyzed intramolecular coupling reaction of (2-halophenyl)-pyridinylmethanone,[6] (d) Pschorr cyclization of 2-nicotinoyl-benzenediazonium salt,[7] and (e) an intramolecular Diels−Alder reaction of (2-alkynylphenyl)(1,2,4-triazin-6-yl)methanone.[8] New efficient synthetic protocols for 2-azafluorenones are still in high demand.

It is known that the labile N−O bond in isoxazoles can be cleaved to form compounds with new functionality. However, the application of isoxazoles as building blocks in organic synthesis is still underdeveloped. Only a few examples employing isoxazoles as the starting materials are known, including the formation of enaminones under reductive conditions (Figure 1, path a),[9] β-keto nitriles under basic conditions (Figure 1, path b),[10] and oxazoles (Figure 1, path c)[11] or imidazoles (Figure 1, path d)[12] under photochemical conditions. To our knowledge, palladium-catalyzed ring-opening reactions of isoxazoles remain unknown. Our ongoing

interest in developing late-transition-metal-catalyzed processes for the preparation of biologically interesting heterocycles[13] has prompted us to explore more facile synthetic approaches for heterocycles with higher molecular complexity. Herein we report a tandem palladium-catalyzed reaction for the synthesis of 2-azafluorenones from halogen-substituted isoxazoles (Figure 1, path e).

Our initial study started from the reaction between isoxazole 1a and methyl vinyl ketone (MVK). After a reaction mixture containing 10 mol % Pd(PPh$_3$)$_4$ and 2 equiv of Li$_2$CO$_3$ in NMP was heated at 150 °C for 16 h, 2-azafluorenone 2a was isolated in 27% yield (Table 1, entry 1).[14] Addition of 1 equiv of n-Bu$_4$NBr increased the yield of 2a to 35% (Table 1, entry 2), so it was used in all subsequent reactions. No 2a was observed when the reaction was carried out at a lower temperature (120 °C; Table 1, entry 3). Changing the solvent from NMP to DMAc gave a similar chemical yield (Table 1, entry 4), while the yield of 2a dropped significantly in DMF (Table 1, entry 5). Screening of palladium catalysts (Table 1, entries 6−10) revealed that the PdBr$_2$ + BINAP combination was optimal (Table 1, entry 10). Addition of 4 Å molecular sieves (80 wt % of 1a) further enhanced the yield of 2a to 62% (Table 1, entry 11). Stronger carbonate bases were found to be less compatible

**Scheme 1. Proposed Reaction Mechanism for the Tandem Palladium Catalysis To Give 2-Azafluorenones**
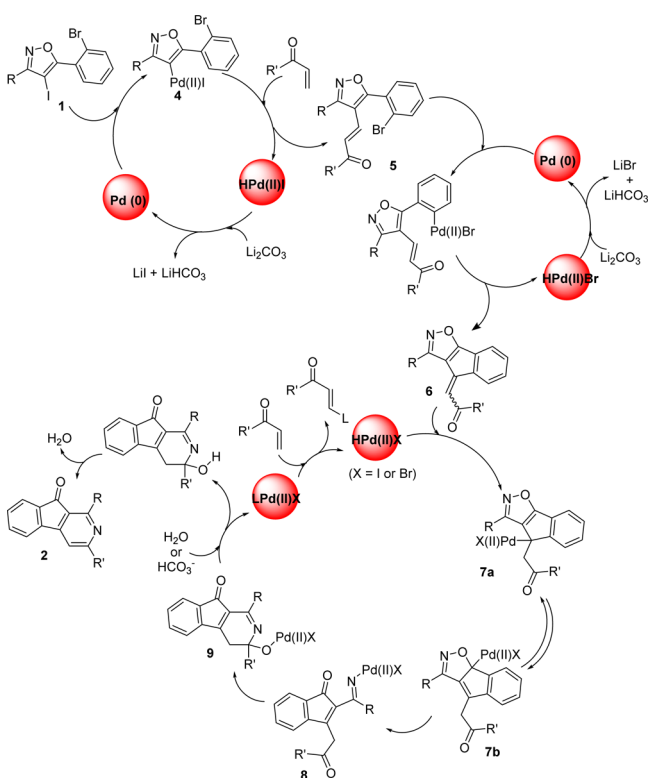
in this reaction and significantly reduced the chemical yield of **2a** (Table 1, entries 12−14).

The reaction scope was investigated using the conditions listed in entry 11 of Table 1. Besides alkyl vinyl ketones (Table 2, entry 1), other Michael acceptors such as acrolein, acrylates, acrylamides, and acrylonitrile (Table 2, entries 1, 2, and 4) all worked well in this reaction. Moderate yields were obtained with alkyl vinyl ketones, acrolein, acrylates, and acrylonitrile, while excellent chemical yields were obtained when acrylamides were employed (Table 2, entry 2). It is worth noting that the reactions between isoxazole **1a** and acrylates or acrylamides all exclusively led to the same product, 3-hydroxy-2-azafluorenone **2d** (Table 2, entry 2). In addition, 3-butoxy-2-azafluorenone **3d** was also observed in these reactions, possibly as a result of in situ etherification between **2d** and n-Bu$_4$NBr.[15] A control experiment between isoxazole **1a** and N,N-dimethylacrylamide showed that no **3d** was formed in the absence of n-Bu$_4$NBr, although this led to a slight sacrifice in the yield of **2d** (Table 2, entry 3). 3-Amino-2-azafluorenones **2f** and **2g** were obtained when acrylonitrile was employed (Table 2, entry 4). Other isoxazoles with different substitution patterns on either the isoxazole ring or the 5-phenyl ring were all well-accommodated in this reaction, even in the absence of n-Bu$_4$NBr (Table 2, entries 3 and 5−8).

A proposed mechanism for the observed tandem catalysis is shown in Scheme 1, starting with an intermolecular Heck reaction between isoxazole **1** and a Michael acceptor to form 4-alkenylisoxazole **5**. A subsequent intramolecular Heck reaction forms indenoisoxazole intermediate **6**. Palladium hydride reinsertion into **6** leads to organopalladium intermediate **7** containing a π-allylpalladium moiety. β-Imino elimination of **7b** opens the isoxazole ring, leading to the formation of indenone intermediate **8**. The latter undergoes an intramolecular

cyclization to generate tricyclic intermediate **9**. Protonation of **9** and subsequent dehydration furnish the final product **2**.[16] It is worth noting that the leaving group in the last step is either an alcohol or an amine when an acrylate or acrylamide, respectively, is employed, leading to the exclusive formation of 3-hydroxy-2-azafluorenone. An imine−enamine tautomerization furnishes the final product when acrylonitrile is used. A Pd(II) complex is regenerated at the end of the rearrangement cycle, which can be converted to the XPd(II)H complex by reaction with a Michael acceptor. Two mechanistically distinct catalytic cycles coexist in this tandem catalysis: a Heck reaction and a rearrangement reaction. While the XPd(II)H complex generated in the Heck reaction needs to be reduced to Pd(0) by a base before entering the next Heck catalytic cycle, it is also essential to maintain a sufficient concentration of XPd(II)H complex in the reaction medium to initiate the rearrangement cycle taking place concurrently in the tandem catalysis. Therefore, it is critical to choose an appropriate base to maintain sufficient concentrations of both XPd(II)H and Pd(0) species in the reaction medium. This agrees with the phenomena we observed during the course of optimizing the reaction conditions, where stronger carbonate bases reduced the chemical yields of the 2-azafluorenone products (Table 1, entries 11−14). More than likely, the concentration of XPd(II)H species was significantly suppressed in these cases.

To develop additional insight into the current tandem catalysis, a presumed intermediate compound, indenoisoxazolylidene-N,N-dimethylacetamide **6a**, was prepared by heating **1a** and N,N-dimethylacrylamide in the presence of Pd(PPh$_3$)$_4$ and K$_2$CO$_3$ at 120 °C (eq 1), reaction conditions presumably not optimal for the rearrangement cycle. A mixture of (E)- and (Z)-**6a** was obtained in 55% yield.[17] When this mixture was subjected to our optimized reaction conditions, the reaction was complete in 4 h, and product **2d** was isolated in 76% yield (eq 2).[18]
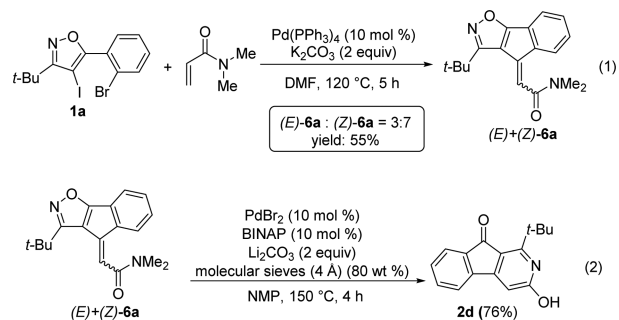
Further investigation revealed that in the absence of n-Bu$_4$NBr, the reaction between **1a** and MVK afforded isoxazole byproduct **10**[19] in 17% yield together with the desired product **2a** (eq 3). The formation of **10** can explain why a lower chemical yield is obtained in the reactions when n-Bu$_4$NBr is absent. In these cases, direct protonation of isoxazolylpalladium intermediate **4** presumably occurs as a side reaction (Scheme 1), leading to 4-H-isoxazoles. On the basis of the preliminary results, we suggest that in the presence of n-Bu$_4$NBr a fast ligand exchange from iodide to bromide on intermediate **4** occurs upon its formation. The presence of a bromide ligand on **4** presumably reduces its direct protonation rate and therefore favors the subsequent Heck reaction.[20]
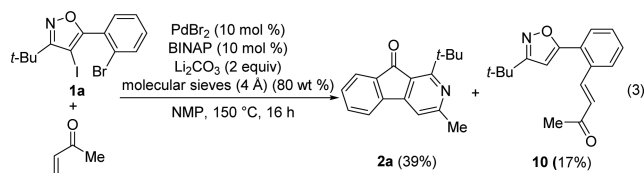
In conclusion, we have developed a new synthetic approach for 2-azafluorenones involving a tandem palladium-catalyzed Heck/Heck-rearrangement reaction from halogen-substituted isoxazoles and Michael acceptors. To the best of our knowledge, this is the first example of a palladium-catalyzed ring-opening reaction of isoxazoles. A key intermediate, indenoisoxazolylidene-*N*,*N*-dimethylacetamide **6a**, was successfully synthesized and converted to the final product, 2-azafluorenone **2d**, under the described optimal reaction conditions. Further investigations incorporating palladium-mediated ring opening reactions of isoxazoles in tandem catalysis and their applications in the synthesis of compounds with new chemical frameworks are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02731.

> X-ray crystallographic data for **2a** (CIF)
> X-ray crystallographic data for **10** (CIF)
> Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yu.chen1@qc.cuny.edu.

Present Address

†Z.S.: School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou 510275, People's Republic of China.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For reviews, see: (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. (c) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem. - Eur. J.* **2009**, *15*, 12168−12179.

(2) For recent examples, see: (a) Li, L.; Herzon, S. B. *Nat. Chem.* **2014**, *6*, 22−27. (b) Chen, Q.-A.; Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 3157−3160.

(3) (a) Wang, H.-L.; Wei, J.-W. *Chin. J. Physiol.* **2012**, *55*, 101−107. (b) Wang, H.-L.; Wang, L.-C.; Wei, J.-W. *Chin. J. Physiol.* **2013**, *56*, 11−17.

(4) (a) Landmesser, T.; Linden, A.; Hansen, H.-J. *Helv. Chim. Acta* **2008**, *91*, 265−284. (b) Li, Y.; Fan, W.; Xu, H.-W.; Jiang, B.; Wang, S.-L.; Tu, S.-J. *Org. Biomol. Chem.* **2013**, *11*, 2417−2420.

(5) (a) Fox, H. H.; Lewis, J. I.; Wenner, W. *J. Org. Chem.* **1951**, *16*, 1259−1270. (b) Fuson, R. C.; Miller, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 3477−3480. (c) Rebstock, A.-S.; Mongin, F.; Trecourt, F.; Queguiner, G. *Tetrahedron* **2003**, *59*, 4973−4977. (d) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588−1594. (e) Shimada, K.; Takata, Y.; Osaki, Y.; Moro-oka, A.; Kogawa, H.; Sakuraba, M.; Aoyagi, S.; Takikawa, Y.; Ogawa, S. *Tetrahedron Lett.* **2009**, *50*, 6651−6653.

(6) Marquise, N.; Harford, P. J.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Gagez, A.-L.; Sable, S.; Picot, L.; Thiery, V.; Wheatley, A. E. H.; Gros, P. C.; Mongin, F. *Tetrahedron* **2013**, *69*, 10123−10133.

(7) Kyba, E. P.; Liu, S.-T.; Chockalingam, K.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 3513−3521.

(8) Hundsdorf, T.; Blyumin, E. V.; Neunhoeffer, H. *Synthesis* **2002**, 2532−2536.

(9) Fogagnolo, M.; Giovannini, P. P.; Guerrini, A.; Medici, A.; Pedrini, P.; Colombi, N. *Tetrahedron: Asymmetry* **1998**, *9*, 2317−2327.

(10) Dominguez, E.; Ibeas, E.; Martinez de Marigorta, E.; Palacios, J. K.; SanMartin, R. *J. Org. Chem.* **1996**, *61*, 5435−5439.

(11) Nunes, C. M.; Reva, I.; Fausto, R. *J. Org. Chem.* **2013**, *78*, 10657−10665.

(12) Pusch, S.; Opatz, T. *Org. Lett.* **2014**, *16*, 5430−5433.

(13) (a) She, Z.; Niu, D.; Chen, L.; Gunawan, M. A.; Shanja, X.; Hersh, W. H.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 3627−3633. (b) Yang, D.; Burugupalli, S.; Daniel, D.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 4466−4472. (c) Long, Y.; She, Z.; Liu, X.; Chen, Y. *J. Org. Chem.* **2013**, *78*, 2579−2588.

(14) The structure of **2a** was confirmed by single-crystal X-ray analysis. For details, see the Supporting Information.

(15) For an example of butylation of phenols by *n*-Bu$_4$NBr, see: Bálint, E.; Greiner, I.; Keglevich, G. *Lett. Org. Chem.* **2011**, *8*, 22−27.

(16) It is also possible that the palladium−nitrogen bond in intermediate **8** is protonated first to give the NH imine, which then undergoes direct intramolecular condensation with the pendant carbonyl group to give product **2**.

(17) The structures of these intermediate compounds were determined by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The *E* and *Z* isomers were determined by nuclear Overhauser effect spectroscopy (for details, see the Supporting Information).

(18) Two control experiments were carried out to estimate the extent of Pd(II) catalysis. In the absence of a palladium catalyst, product **2d** was isolated in 32% yield after 4 h, and 26% of starting material **6a** was recovered after column chromatography. On the other hand, when Pd$_2$(dba)$_3$ was employed as the catalyst, product **2d** was isolated in 51% yield after 4 h, and 24% of starting material **6a** was recovered after column chromatography. These facts suggest the presence of a slower rearrangement pathway that is not catalyzed by Pd(II), with the possible adventitious oxidation of Pd(0) from Pd$_2$(dba)$_3$ to Pd(II) to account for the higher yield in that control reaction.

(19) The structure of **10** was confirmed by single-crystal X-ray analysis. For details, see the Supporting Information.

(20) For a review of halide effects in transition-metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.