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Palladium-Catalyzed Annulation of Arynes by 2-Halobenzaldehydes: Synthesis of Fluoren-9-ones

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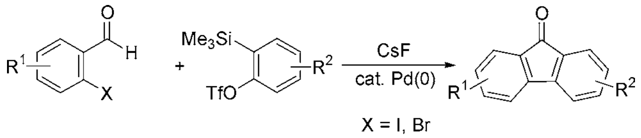
ABSTRACT



Arynes, generated *in situ* from 2-(trimethylsilyl)aryl triflates and CsF, undergo annulation by *o*-haloarenecarboxaldehydes in the presence of a Pd catalyst, providing a useful new method for the synthesis of fluoren-9-ones in good yields.

The transition-metal-catalyzed transformations of arynes have recently received considerable attention. Pioneering work in this area involved the cyclotrimerization of arynes[1] and the cocyclization of arynes with alkynes.[2] More recently, metal-catalyzed carbonylative cycloadditions of arynes[3] and the cocyclotrimerization of arynes with bicyclic alkenes[4] and allenes[5] have been reported. Great progress has also been made in the addition of element−element σ-bonds to arynes, including Si−Si,[6] C−Sn,[7] and Sn−Sn[8] bonds. There are also a few examples of the addition of π-allylpalladium compounds to arynes.[9]

The palladium-catalyzed annulation of alkynes by functionally substituted aryl halides has proven to be a very efficient method for the construction of a wide variety of heterocycles and carbocycles.[10] However, similar carbopalladation reactions of arynes are unprecedented to the best of our knowledge.[11] Our continuing interest in palladium-catalyzed annulation reactions prompted us to explore such possibilities. Herein, we report the first example of the palladium-catalyzed annulation of arynes by *o*-halobenzaldehydes.[12] This provides a convenient synthesis of fluoren-9-ones, which are of considerable interest because of their important biomedical applications[13] and their use as key synthetic intermediates.[14]

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(1) (a) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **1999**, *1*, 1555. (c) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **2000**, *2*, 1629.

(2) (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Synlett* **2000**, 1061. (c) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944. (d) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Eur. J. Org. Chem.* **2003**, 1238. (e) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436.

(3) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686.

(4) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 8445.

(5) Hsieh, J.-C.; Rayabarapu, D. K.; Cheng, C.-H. *Chem. Commun.* **2004**, 532.

(6) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2003**, *125*, 6638.

(7) Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. *Chem. Commun.* **2001**, 1880.

(8) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052.

(9) (a) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729. (b) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem.* Soc. **2000**, *123*, 7280. (c) Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821. (d) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921.

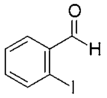
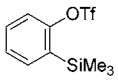
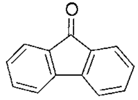
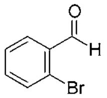
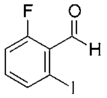
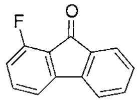
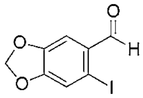
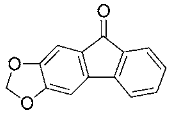
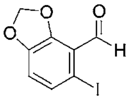
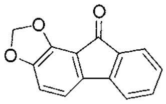
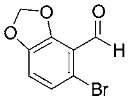
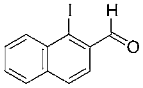
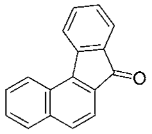
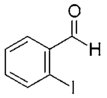
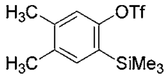
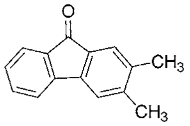
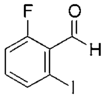
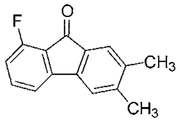
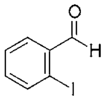
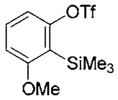
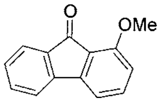
(10) For reviews, see: (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (b) Larock, R. C. Palladium-Catalyzed Annulation. In *Perspectives in Organopalladium Chemistry for the XXI Century*; Tsuji, J., Ed.; Elsevier Press: Lausanne, Switzerland, 1999; pp 111−124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.

(11) Our own group has reported the synthesis of carbazoles and dibenzofurans by the cross-coupling of *o*-iodoanilines and *o*-iodophenols with arynes, followed by palladium-catalyzed cyclization. However, this process does not involve the carbopalladation of arynes. See: Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739.

(12) For the palladium-catalyzed annulation of internal alkynes by *o*-halobenzaldehydes, see: Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.

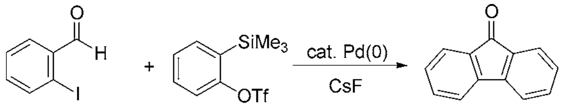
10.1021/ol0514597 CCC: $30.25

Table 1. Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Annulation of Silylaryl Triflates by *o*-Haloarenecarboxaldehydes[a]

	aryl halide		silylaryl triflate		product		% yield
1		**1**		**2**		**3**	75
2		**4**		**2**		**3**	73[b]
3		**5**		**2**		**6**	82
4		**7**		**2**		**8**	56
5		**9**		**2**		**10**	72
6		**11**		**2**		**10**	50
7		**12**		**2**		**13**	48
8		**1**		**14**		**15**	71
9		**5**		**14**		**16**	73
10		**1**		**17**		**18**	61[c]

[a] All reactions were run under the following conditions unless otherwise specified: 0.30 mmol of *o*-halobenzaldehyde, 5 equiv of silylaryl triflate, 5 equiv of CsF, 5% of Pd(dba)$_2$, and 5% of P(*o*-tolyl)$_3$ in 4 mL of 1:1 MeCN/toluene were heated at 110 °C for 12 h. [b] This reaction needed 24 h to reach completion, and the yield was determined by GC-MS. [c] Yield of the other isomer was 7% according to gas chromatographic analysis.

The high reactivity[15] and short lifetime of benzyne and other arynes suggest that their use as a component of a catalytic reaction might be difficult. Therefore, our preliminary efforts focused on the optimization of reaction conditions for the reaction of 2-iodobenzaldehyde (**1**) with silylaryl triflate **2**, which we have observed to afford fluoren-9-one (**3**) (eq 1).



1 **2** **3** (1)

Compound **1** (0.30 mmol) was initially treated with 3 equiv of silylaryl triflate **2** plus 3 equiv of CsF, a combination known to generate benzyne,[16] along with 5% Pd(OAc)$_2$ and 5% P(*o*-tolyl)$_3$ as the catalyst in 4 mL of MeCN at 70 °C. The desired product **3** was obtained in a 36% yield. The yield was improved to 51% when using 2 mL of toluene and 2 mL of MeCN as the solvent. Other solvents such as THF, DMF, and toluene alone all gave poor yields (0−24%). The choice of base was also crucial for the success of the reaction. Replacement of CsF with KF or utilizing NEt$_3$ or

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(13) (a) Tierney, M. T.; Grinstaff, M. W. *J. Org. Chem.* **2000**, *65*, 5355. (b) Han, Y.; Bisello, A.; Nakamoto, C.; Rosenblatt, M.; Chorev, M. *J. Pept. Res.* **2000**, *55*, 230. (c) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. *Biorg. Med. Chem. Lett.* **1999**, *9*, 3225. (d) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679. (e) Jones, W. D.; Ciske, F. L.; Dinerstein, R. J.; Diekema, K. A. U.S. Patent 6,004, 959, 1999.

(14) (a) Koyama, H.; Kamikawa, T. *Tetrahedron Lett.* **1997**, *38*, 3973. (b) Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320.

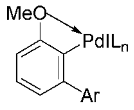
(15) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

(16) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

Cs_2CO_3 as a base together with CsF greatly decreased the yield. Using pyridine, none of the desired product was generated at all. Control experiments revealed that in the absence of the palladium catalyst or the CsF, no fluorenone **3** was obtained. Variation of the Pd catalyst and ligands had a minimal effect. For example, 5% $Pd(dba)_2$ with 5% P(*o*-tolyl)$_3$ improved the yield to 59%. Similar yields (50−57%) were obtained using $Pd(dba)_2$ plus dppf or 2-(dicyclohexylphosphino)biphenyl. The ligand dppe provided only a 38% yield of **3**. The yield was dramatically improved to 75% when 5 equiv of silylaryl triflate **2** and 5 equiv CsF were used at 110 °C. Therefore, the following reaction conditions were chosen as our "optimal" conditions: 0.30 mmol of aryl halide, 5 equiv of the silylaryl triflate, 5 equiv of CsF, 5% $Pd(dba)_2$, 5% P(*o*-tolyl)$_3$ in 4 mL of 1:1 toluene/MeCN at 110 °C for 12 h.

This palladium-catalyzed annulation reaction was successfully extended to other *o*-haloarenecarboxaldehydes and substituted arynes (Table 1). When *o*-bromobenzaldehyde was employed as the aryl halide, a yield comparable to that of *o*-iodobenzaldehyde was obtained, although a much longer reaction time was required (compare entries 1 and 2, Table 1). The addition of a fluorine substituent on the aromatic ring of the aldehyde improved the yield to 82% (entry 3). This could be because the electron-withdrawing fluorine facilitates oxidative addition of the aryl iodide to the palladium and at the same time increases the electrophilicity of the carbonyl group (see the later mechanistic discussion). On the other hand, the reaction of 2-iodo-4,5-methylenedioxybenzaldehyde (**7**) with triflate **2** generated fluorene-9-one derivative **8** in only a 56% yield (entry 4). One might be tempted to attribute this to the electron-rich nature of the aromatic ring. The corresponding 2-bromobenzaldehyde afforded an even lower yield. However, electron-rich 2-iodo-5,6-methylenedioxybenzaldehyde (**9**) reacts smoothly with triflate **2** to provide the desired product **10** in a 72% yield (entry 5). Even annulation with the corresponding aryl bromide **11** proceeded without problems in a moderate yield (entry 6). The reaction was also successfully applied to naphthaldehyde **12** (entry 7). The slightly lower yield here might be due to the fact that the iodide is located on the sterically hindered 1 position of the naphthalene, thereby slowing the oxidation−addition to Pd and/or hindering aryne annulation.

In addition to **2**, other substituted aryne precursors have also been successfully exploited in this process. Thus, triflate **14** with two methyl groups on the phenyl ring furnished products **15** and **16** in 71 and 73% yields, respectively (entries 8 and 9). Reaction with 3-methoxybenzyne (from triflate **17**) showed good regioselectivity, affording the two possible isomeric fluoren-9-ones in a 9:1 ratio as determined by GC-MS analysis. Compound **18** is the major product as determined by comparison of its ^1H and ^{13}C NMR spectra with those of the known compound.[17] Fluoren-9-one **18** is apparently formed by preferential formation of intermediate **19**, which may be favored due to coordination of the methoxy group to Pd.[3,18] Intermediate **19** is also the product one would expect from the more anionic aryl moiety of ArPdX adding to the more remote carbon of the aryne. In addition, as observed in the carbopalladation of alkynes,[10] Pd may prefer to add to the more hindered end of the aryne, which is *ortho* to the methoxy group.



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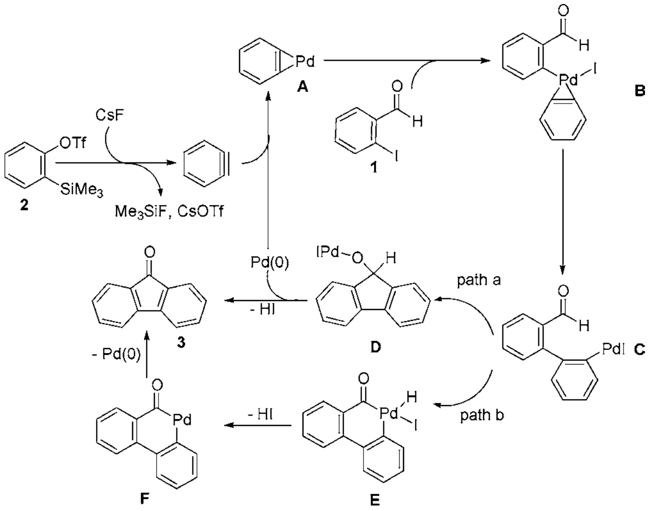
On the basis of the known chemistry of organopalladium compounds and alkynes, the following mechanism is proposed (Scheme 1; ligands are omitted for simplicity). First, the aryne generated from the triflate coordinates with Pd(0), affording palladacycle **A**. Oxidative addition of the aryl iodide to **A** generates arylpalladium(IV) complex **B**. Reductive elimination affords a new arylpalladium intermediate **C**. Intermediate **C** can add to the carbonyl group[19] and subsequently undergo β-hydride elimination (path a), or the aldehyde C−H bond may oxidatively add[20] to the palladium to produce an organopalladium(IV) intermediate **E**, which subsequently undergoes rapid reductive elimination to provide the desired product and regenerate the Pd(0) catalyst (path b). The exact pathway is unclear.

Scheme 1



The involvement of an aryne in this catalytic reaction is strongly supported by the results of the reaction between **1** and **20**, which affords a 71% yield of a mixture of two regioisomeric products **21** and **22** in a nearly 1:1 ratio as

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[17] Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.

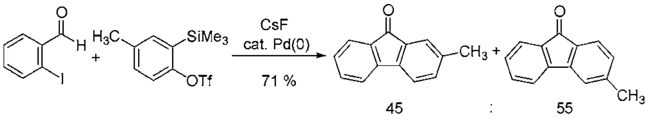
[18] (a) Takeuchi, R.; Yasue, H. *J. Org. Chem.* **1993**, *58*, 5386. (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

[19] (a) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089. (b) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545.

[20] Wei, L.; Wei, L.; Pan, W.; Wu, M. *Synlett* **2004**, 1497.

determined by GC-MS and ^{1}H NMR spectroscopic analysis (Scheme 2). This observation indicates that the aryl group of the starting aryl halide adds about equally to the two carbons originally attached to the silyl and OTf groups, in agreement with the formation of an aryne from **20** prior to reaction with the aldehyde **1**.

Scheme 2



1 **20** **21** **22**

In conclusion, we have developed a new palladium-catalyzed annulation reaction of arynes by 2-haloarenecarboxaldehydes. This method provides an efficient synthesis of substituted fluoren-9-ones from readily available starting materials. Extension of this method to the synthesis of other biological interesting heterocycles and carbocycles and the exploration of similar protocols with other functionally substituted haloarenes and arynes are underway.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institute of General Medical Sciences (GM 070620) for partial support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc., for donating the palladium acetate.

Supporting Information Available: General experimental procedures and spectral data for all of the starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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