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Synthesis of Fluoro- and Perfluoroalkyl Arenes via Palladium-Catalyzed [4 + 2] Benzannulation Reaction

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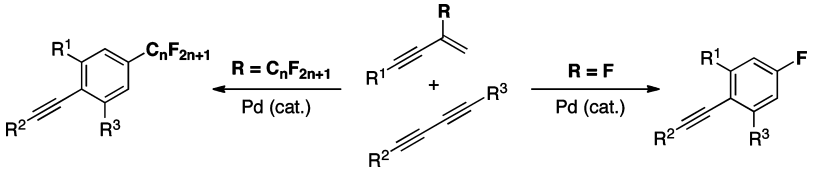
ABSTRACT



An efficient entry into densely substituted fluorinated and perfluoroalkylated benzene derivatives via chemo- and regioselective Pd-catalyzed [4 + 2] cross-benzannulation is presented. The synthetic utility of these products for the synthesis of various aromatic and heteroaromatic compounds is also demonstrated. This strategy offers a viable and quite general alternative to existing fluorination and perfluoroalkylation methods for securing these valuable molecules.

Due to their unique physical, chemical, and biological properties, fluoride and perfluoroalkyl-containing aromatic compounds are garnering increasing attention in various research areas.[1] In recent years, substantial progress toward the synthesis of aryl fluorides **1** has been achieved[2] (Scheme 1). A variety of transition metal mediated strategies, as well as metal-free procedures, have been added to the traditional fluorination methods, such as Balz–Schiemann and aromatic nucleophilic substitution reactions. All these approaches employ fluorination of pre-existing aromatic precursors with either nucleophilic or electrophilic fluorine sources. On the other hand, cycloaddition methods serve as a powerful tool set for the rapid assembly of aromatic cores.[3] Although several examples are known for introduction of perfluoroalkyl groups[4] onto a benzene ring via a [2 + 2 + 2] cycloaddition reaction of perfluoroalkylated alkynes,[5,6] to the best of our knowledge, construction of aryl fluorides via similar methods has not been previously described,[7] presumably due to

(1) For selected reviews, see: (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (d) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501.

(2) For reviews, see: (a) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225. (b) Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8610. (c) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (d) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, *11*, 1804. (e) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (f) Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012**, *45*, 67. (g) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.

(3) For selected reviews, see: (a) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830. (b) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(4) For selected reviews on trifluoromethylation of aromatic compounds, see: (a) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (b) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. See also ref 2d, 2e.

(5) For Rh-catalyzed [2 + 2 + 2] cycloaddition, see: (a) Garcia, J. J.; Sierra, C.; Torrens, H. *Tetrahedron Lett.* **1996**, *37*, 6097. (b) Tanaka, K.; Hara, H.; Nishida, G.; Hirano, M. *Org. Lett.* **2007**, *9*, 1907. (c) Konno, T.; Moriyasu, K.; Kinugawa, R.; Ishihara, T. *Org. Biomol. Chem.* **2010**, *8*, 1718. For Ru-catalyzed [2 + 2 + 2] cycloaddition, see: (d) Kawatsura, M.; Yamamoto, M.; Namioka, J.; Kajita, K.; Hirakawa, T.; Itoh, T. *Org. Lett.* **2011**, *13*, 1001. For Ni-catalyzed [2 + 2 + 2] cycloaddition, see: (e) Müller, C.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **2002**, *21*, 1975.

(6) For synthesis of perfluoroalkylarenes using Diels–Alder reaction, see: (a) Wong, H. N. C. *Synthesis* **1984**, 787. (b) Abubakar, A.; Booth, B.; Suliman, N.; Tipping, A. *J. Fluorine Chem.* **1992**, *56*, 359. (c) Chambers, R. D.; Roche, A.; Rock, M. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1095. (d) Zhu, G.-D.; Staeger, M. A.; Boyd, S. A. *Org. Lett.* **2000**, *2*, 3345.

(7) For formation of aryl fluorides via Dewar benzene intermediate, see: (a) Hanamoto, T.; Koga, Y.; Kawanami, T.; Furuno, H.; Inanaga, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3582. (b) Hanamoto, Y.; Koga, Y.; Kawanami, T.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2006**, *47*, 493. (c) Yao, Z.-K.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 10864.

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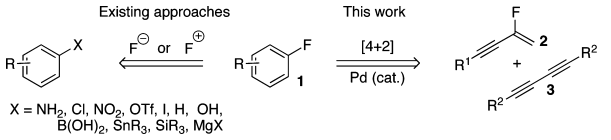
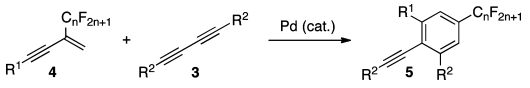
Scheme 1. Alternative Strategies toward Fluoroarenes

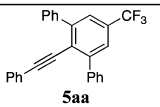
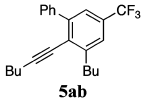
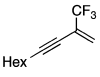
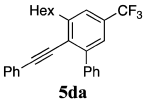
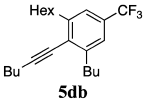
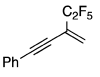
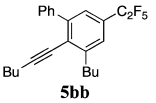
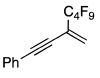
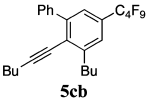
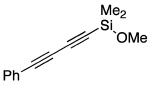
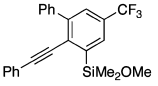


the explosive nature of the required starting fluoro alkynes.[8] We envisioned that the Pd-catalyzed [4 + 2] cross-benzannulation reaction between conjugated enynes and diynes[9,10] might provide an alternative route for the facile synthesis of fluorinated benzene cores (Scheme 1). In this case, the fluorine atom could be introduced at the alkene moiety of an enyne coupling partner, thus avoiding the employment of fluoro alkynes. Importantly, compared with other vinyl halides, vinyl fluorides are less reactive toward the oxidative addition of low-valent transition metals,[11] which would allow the Pd(0)-catalyzed benzannulation process of fluoro enynes **2** to proceed without accompanying defluorination. Herein, we wish to report an efficient synthesis of aryl fluorides, as well as perfluoroalkyl arenes, from acyclic precursors employing a Pd-catalyzed [4 + 2] cycloaddition strategy.

To test our benzannulation strategy for fluoroarenes, we first examined the cycloaddition of trifluoromethylenynes with the aid of a recently developed highly efficient catalytic system.[12] Gratifyingly, a cross-benzannulation reaction between enyne **4a** and diphenyldiyne **3a**, in the presence of 1% of a Pd-catalyst, afforded the desired

Table 1. Benzannulation toward Perfluoroalkylbenzenes[a]



entry	enyne	diyne	product	yield (%)[b]
1	 **4a**	 **3a**	 **5aa**	84
2	**4a**	 **3b**	 **5ab**	76
3	 **4d**	**3a**	 **5da**	89
4	**4d**	**3b**	 **5db**	72
5	 **4b**	**3b**	 **5bb**	77
6	 **4c**	**3b**	 **5cb**	87
7	**4a**	 **3c**	 **5ac**	78[c]

[a] Reaction conditions: **4** (0.6 mmol), **3** (0.5 mmol), IPrPdAllCl (1 mol %), (2-furyl)$_3$P (2 mol %), CsOPiv (2 mol %), toluene (1 M), 100 °C, 16−24 h. [b] Isolated yields, %. [c] Reaction conditions: **4a** (0.75 mmol), **3c** (0.5 mmol), $Pd_2(dba)_3$ (5 mol %), (2-furyl)$_3$P (10 mol %), toluene (1 M), 100 °C; NMR yield, %.

trifluoromethyl-containing arene **5aa** in 84% yield in a highly regio- and chemoselective manner (Table 1, entry 1). Analogously, the reaction between enyne **4a** and dialkyl-substituted diyne **3b** proceeded with good efficiency (entry 2). Employment of alkyl substituted enyne **4d** afforded the corresponding trifluoromethylarene **5da** in high yield (entry 3). However, 3,5-dialkyl substituted trifluoromethylarene **5db** was obtained in 72% yield along with 15% of the homo-benzannulation product of **4d** (entry 4). Presumably, the high reactivity of enyne **4d** and the low reactivity of diyne **3b** both accounted for this result. Similarly to trifluoromethylarenes, arylalkynes bearing a perfluoroalkyl chain can also be obtained with high efficiency via the benzannulation reaction of enynes **4b** and **4c** (entries 5, 6). Importantly, unsymmetrically substituted silyldiyne **3c** reacted with enyne **4a** to produce trifluoromethylarene **5ac** (entry 7) with perfect regioselectivity. Base-free reaction conditions were employed in this case to avoid loss of the fragile alkynylsilyl ether functionality. Although hydrolytically unstable, product **5ac** possesses a valuable *ortho*-alkynyl arylsilyl ether functionality that can

(8) (a) Middleton, W. J.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 803. (b) Viehe, H. G.; Merényi, R.; Oth, J. F. M.; Valange, P. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 746.

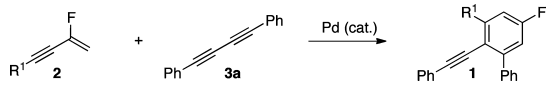
(9) For transition-metal-free [4 + 2] benzannulation, see: (a) Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. (b) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (c) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917. For Pd-catalyzed [4 + 2] benzannulation, see: (d) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970. (e) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313. (f) Gevorgyan, V.; Sadayori, N.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 8603. (g) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391. (h) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818. For Co-catalyzed [4 + 2] benzannulation, see: (i) Pünner, F.; Hilt, G. *Chem. Commun.* **2012**, 3617.

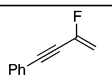
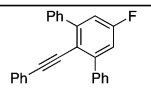
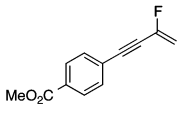
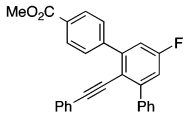
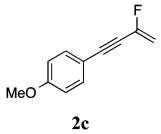
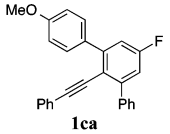
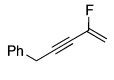
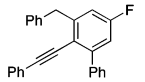
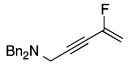
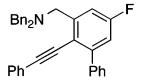
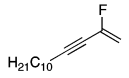
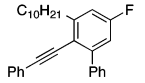
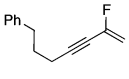
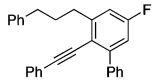
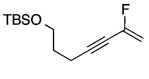
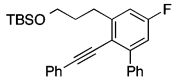
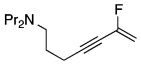
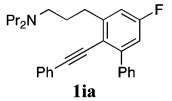
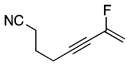
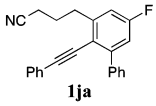
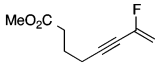
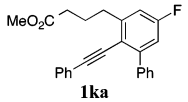
(10) For synthetic application, see: (a) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1244. (b) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 568. (c) Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338. (d) Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D. J.; Gevorgyan, V. *J. Org. Chem.* **2003**, *68*, 6251. (e) Nakao, Y.; Hirata, Y.; Ishihara, S.; Oda, S.; Yukawa, T.; Shirakawa, E.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 15650. (f) Gevorgyan, V.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2743. (g) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. (h) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (i) Liu, J. X.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 4201. (j) Gevorgyan, V.; Tando, K.; Uchiyama, N.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7022. (k) Lewis, F. D.; Zuo, X.; Gevorgyan, V.; Rubin, M. *J. Am. Chem. Soc.* **2002**, *124*, 1366. (l) Lewis, F. D.; Sajimon, M. C.; Zuo, X.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 10447. For cascade reactions, see: (m) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. (n) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347.

(11) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344.

(12) Zatolochnaya, O. V.; Galenko, A. V.; Gevorgyan, V. *Adv. Synth. Catal.* **2012**, *354*, 1149.

Table 2. Scope of Enynes for the Synthesis of Fluoroarenes[a]



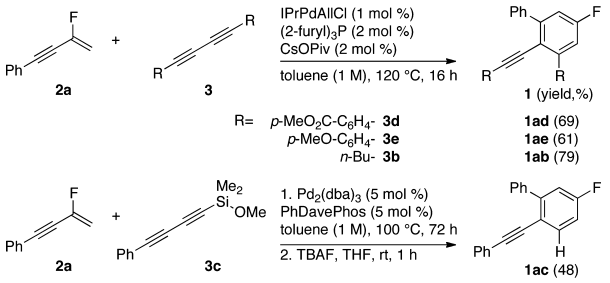
entry	enyne	product	time (h)	yield (%)[b]
1	 **2a**	 **1aa**	16	85
2	 **2b**	 **1ba**	16	78
3	 **2c**	 **1ca**	24	51
4	 **2d**	 **1da**	20	57
5	 **2e**	 **1ea**	16	84
6	 **2f**	 **1fa**	20	71
7	 **2g**	 **1ga**	20	86
8	 **2h**	 **1ha**	20	83
9	 **2i**	 **1ia**	16	82
10	 **2j**	 **1ja**	24	60
11	 **2k**	 **1ka**	24	62

[a] Reaction conditions: **2** (0.6 mmol), **3** (0.5 mmol), IPrPdAllCl (1 mol %), (2-furyl)$_3$P (2 mol %), CsOPiv (2 mol %), toluene (1 M), 120 °C, 16−24 h. [b] Isolated yields, %.

be further utilized in the synthesis of various aromatic scaffolds (*vide infra*).

Encouraged by these results, we turned our attention to the synthesis of aryl fluorides via the benzannulation of fluoro-containing enynes **2**. To our delight, 3-fluoro-1-phenylenyne **2a** underwent a facile benzannulation reaction with diphenyldiyne **3a**, thus giving access to

Scheme 2. Scope of Diynes for the Synthesis of Fluoroarenes



p-alkynylaryl fluoride **1aa** in 85% yield (Table 2, entry 1). Likewise, fluoro enyne **2b** provided the cross-benzannulation product **1ba** in good yield (entry 2). As expected, enyne **2c** bearing an electron-donating group delivered the corresponding fluoroarene with moderate efficiency[12] (entry 3). Substrates **2d**,**e** substituted at the propargylic position were smoothly converted to the corresponding fluoroarene derivatives (entries 4, 5). Similarly, alkyl substituted fluoro enynes were competent substrates for the benzannulation reaction (entries 6, 7). Differently substituted alkyl enynes possessing valuable functionalities, such as silyloxy (entry 8), amino (entries 5, 9), cyano (entry 10), and ester (entry 11) groups, were well tolerated under these reaction conditions.

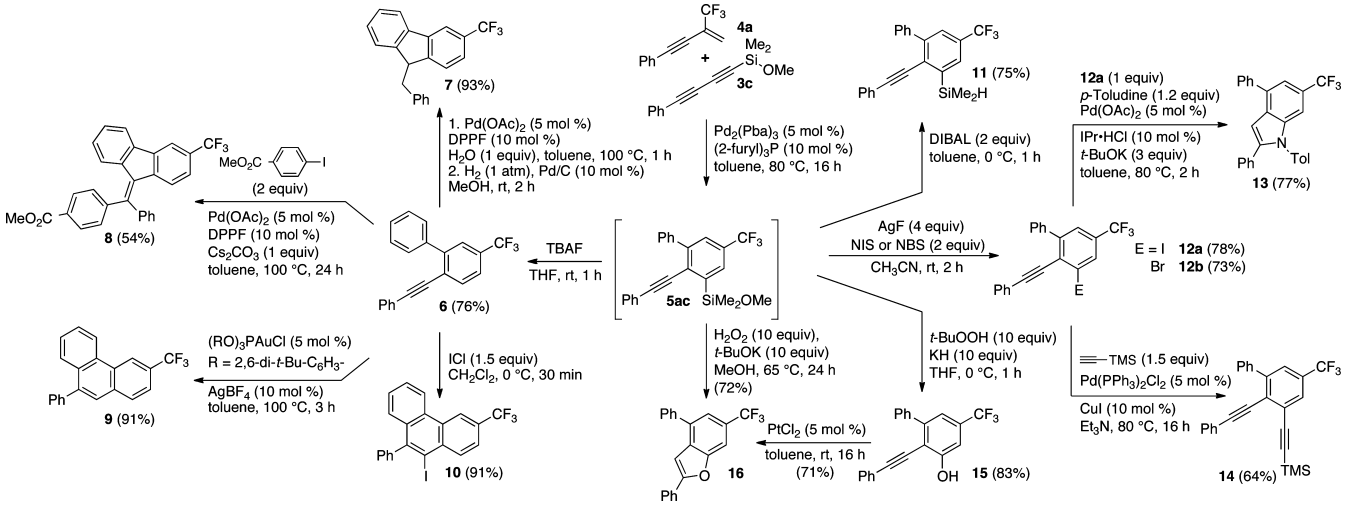
Next, the reactivity of different diynes toward this benzannulation with enyne **2a** was examined (Scheme 2). Thus, employment of either electron-deficient (**3d**) or electron-rich (**3e**) symmetrical diaryldiynes, as well as dialkyl-substituted diyne (**3b**), led to the formation of fluorinated arenes in good yields. 3-Fluoroenyne **2a** also underwent benzannulation with unsymmetrically substituted silyldiyne **3c**. In this case, the hydrolytically unstable product was isolated as the desilylated adduct **1ac**, after treatment with TBAF in a one-pot fashion.

Notably, this benzannulation strategy, which leads to alkynyl-containing arenes, offers a unique opportunity for accessing various aromatic and heteroaromatic scaffolds. It seems particularly attractive for the synthesis of molecules possessing a modifiable silyl group at the aryl ring. Accordingly, we explored further transformations of trifluoromethyl-containing *o*-alkynylsilyl ether **5ac**, the product of the benzannulation of enyne **4a** and diyne **3c** (Table 1, entry 7). Given the hydrolytical instability of **5ac**, it was used crude.[13] *ortho*-Alkynylbiaryls are valuable substrates in the synthesis of polycyclic aromatic scaffolds.[14] Thus, benzannulation product **5ac** was desilylated to afford the corresponding *o*-alkynylbiaryl **6** in 76% yield via a one-pot operation (Scheme 3). It was found that **6**

(13) See Supporting Information for details.

(14) (a) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (b) Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2009**, *351*, 1101. (c) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (d) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556. (e) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677. (f) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511.

Scheme 3. Synthesis of Trifluoromethyl-Containing Aromatic and Heteroaromatic Compounds



underwent smooth Pd-catalyzed 5-*exo*-dig cyclization[14a] followed by hydrogenation to form the corresponding fluorene **7**. Alternatively, arylative 5-*exo*-dig cyclization[14b] of **6** afforded unsymmetrically substituted fluorene **8** as a single stereoisomer. Electrophilic 6-*endo*-dig cyclization[14c,d] under gold catalysis delivered the CF_3-containing phenanthrene **9** in excellent yield. Iodo-containing phenanthrene **10** was efficiently assembled from **6** via an ICl-induced 6-*endo*-dig cyclization.[14e,f]

Naturally, we were interested in exploring the advantages provided by the silyl group located at the *ortho*-position to the triple bond. Thus, reduction of the silyl ether group with DIBAL-H provided access to hydrosilane **11** in 75% yield over the two-step sequence. This compound represents not only a hydrolytically stable analog of **5ac** but also a potential substrate for the synthesis of benzosilols.[15] Alternatively, silver fluoride mediated electrophilic halogenation of **5ac** afforded haloarenes **12a** and **12b** in good yields. *ortho*-Alkynyliodide **12a** was efficiently converted to a densely substituted indole **13** via the Pd-catalyzed amination/cyclization sequence.[16] Notably, the overall procedure allows for the synthesis of 6-substituted indole in just three steps starting from acyclic precursors **4a** and **3c**. Additionally, Sonogashira cross-coupling of **12a** with trimethylsilylacetylene afforded the Bergman cyclization precursor **14**. Finally, the Tamao oxidation of **5ac** under mildly basic conditions offered an access toward *o*-alkynylphenol **15**, leaving the triple bond unaffected. Further electrophilic cyclization under Pt-catalysis[17] delivered the benzofuran **16**. Interestingly, under forcing oxidation conditions, an unprecedented direct transformation of *o*-alkynylsilylbenzene **5ac** into benzofuran **16** was observed.

In conclusion, an efficient and selective method for the synthesis of fluoro- and perfluoroalkylaromatic compounds via the Pd-catalyzed [4 + 2] cross-benzannulation reaction has been developed. This cycloaddition strategy proved to be effective for the rapid construction of aromatic fluorides from easily available acyclic starting materials. Significantly, many of these products can be easily transformed into a variety of diverse aromatic and heteroaromatic structures.

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Supporting Information Available. Experimental procedure and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Yamaguchi, S.; Xu, C.; Tamao, K. *J. Am. Chem. Soc.* **2003**, *125*, 13662. (b) Ilies, L.; Tsuji, H.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4240. (c) Ilies, L.; Tsuji, H.; Nakamura, E. *Org. Lett.* **2009**, *11*, 3966.

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The authors declare no competing financial interest.