Communications

Fluorostannylation

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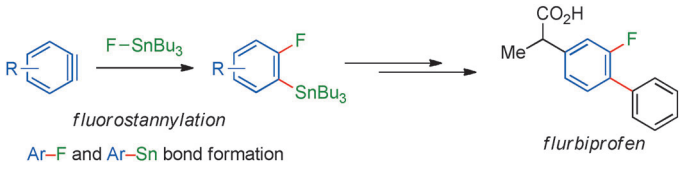
Synchronous Ar—F and Ar—Sn Bond Formation through Fluorostannylation of Arynes



An aryne insertion into the F—Sn bond of tributyltin fluoride leads to the synchronous formation of Ar—F and Ar—Sn bonds to afford diverse 2-fluoroarylstannanes straightforwardly. The formal total synthesis of flurbiprofen by using a fluorostannylation product is also reported.

Fluorostannylation

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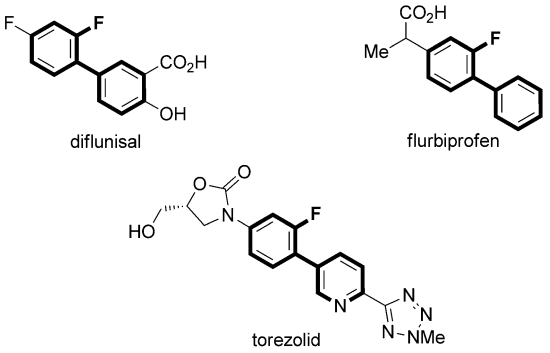
Synchronous Ar–F and Ar–Sn Bond Formation through Fluorostannylation of Arynes**

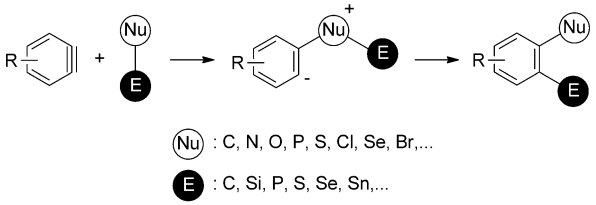
Hiroto Yoshida, Ryuma Yoshida, and Ken Takaki*

A lot of effort has recently been devoted to the development of efficacious methods for incorporating fluorine atoms into aromatic frameworks,[1] because fluorinated aromatic compounds are extensively utilized as pharmaceuticals, agrochemicals, etc.[2] Although aryl fluorides of various structures are accessible by pyrolysis of arenediazonium tetrafluoroborates (the Balz–Schiemann reaction),[3] nucleophilic aromatic substitution,[4] electrophilic fluorination of aryl Grignard reagents,[5] and transition-metal-promoted fluorination[6] and deoxyfluorination of phenols,[7] the search for potent Ar–F bond-forming reactions is still of great significance in synthetic organic chemistry. Among the diverse aryl fluorides, 2-fluorobiaryl motifs are of particular importance,[5c] as they constitute a valuable class of biologically active compounds including diflunisal, flurbiprofen, and torezolid[8] (Scheme 1).



Scheme 1. Representative biologically active compounds containing a 2-fluorobiaryl motif.

We have been studying aryne insertion into σ bonds between a nucleophile and an electrophile, whereby nucleophilic attack to arynes triggers the insertion reaction (Scheme 2).[9,10] Although a variety of σ bonds can be added across arynes to afford diverse *ortho*-disubstituted arenes in a straightforward manner, to the best of our knowledge, there has been no precedent for the introduction of fluorine onto



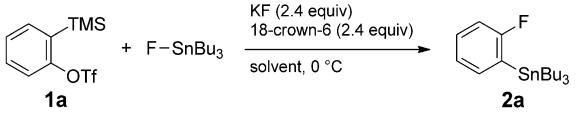
Scheme 2. Insertion of arynes into σ bonds between a nucleophile and an electrophile. Nu = nucleophile, E = electrophile.

aromatic rings by an insertion reaction, probably owing to the hard/soft mismatch between fluorine atoms and arynes.[11] Herein, we report an unprecedented aryne insertion reaction into F-containing σ bonds by the use of a tin fluoride.[12] The reaction (fluorostannylation) involves synchronous Ar–F and Ar–Sn bond formation and produces various 2-fluoroarylstannanes,[13] which are versatile intermediates for the synthesis of 2-fluorobiaryls by the Migita–Kosugi–Stille reaction.

We first investigated the reaction of benzyne (from 2-(trimethylsilyl)phenyl triflate **1a** and KF/[18]crown-6)[14] with tributyltin fluoride in DME at 0 °C; Ar–F and Ar–Sn bonds were formed at adjacent positions of the aromatic ring to give tributyl(2-fluorophenyl)stannane (**2a**) in 97% yield (Table 1, entry 1). The use of diethyl ether as a solvent resulted in a slower reaction (Table 1, entry 2), and the yield of **2a** was lower for the reaction in THF (Table 1, entry 3).

We next investigated the scope of the reaction by using various substituted arynes under the optimized reaction conditions (Table 2). Symmetrical arynes, such as 4,5-dimethylbenzyne (from **1b**) and cyclopentane-condensed aryne (from **1c**), underwent efficiently the fluorostannylation to

Table 1: Reaction conditions for fluorostannylation of benzyne.[a]



Entry	Solvent	*t* [h]	Yield [%][b]
1	DME	6	97
2	Ether	122	97
3	THF	6.5	83

[a] Reaction conditions: **1a** (0.12 mmol, 1.2 equiv), F–$SnBu_3$ (0.10 mmol, 1 equiv), KF (0.24 mmol, 2.4 equiv), [18]crown-6 (0.24 mmol, 2.4 equiv), solvent (1 mL). [b] Yield of isolated **2a**. DME = 1,2-dimethoxyethane, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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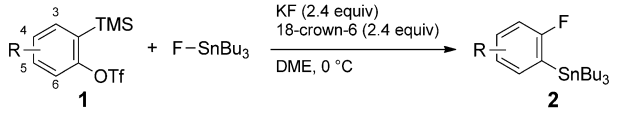
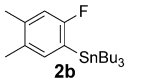
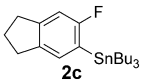
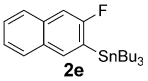
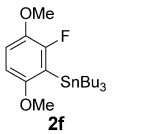
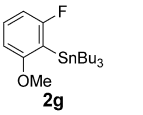
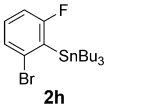
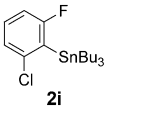
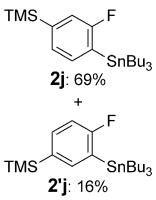
Table 2: Fluorostannylation of arynes.[a]



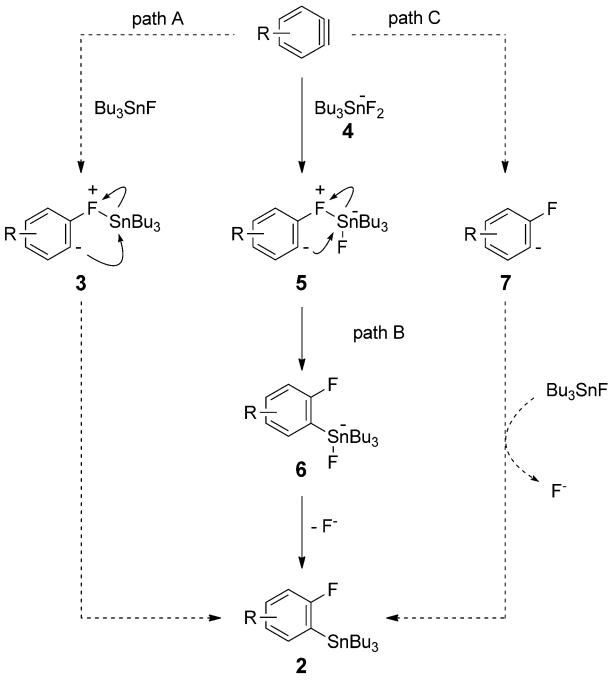
1 1.2 : 1 **2**

Entry	R	*t* [h]	Yield [%][b]	Product
1	4,5-Me_2 (**1b**)	52	78	 **2b**
2	4,5-$(CH_2)_3$ (**1c**)	72	71	 **2c**
3	4,5-F_2 (**1d**)	47	50	 **2d**
4	4,5-$(CH)_4$ (**1e**)	26	46	 **2e**
5	3,6-$(MeO)_2$ (**1f**)	6	81	 **2f**
6	3-MeO (**1g**)	27	76	 **2g**
7	6-Br (**1h**)	8	43	 **2h**
8	6-Cl (**1i**)	7	41	 **2i**
9	4-TMS (**1j**)	31	85	 **2j**: 69% + **2′j**: 16%

[a] Reaction conditions: **1** (0.12 mmol, 1.2 equiv), F–$SnBu_3$ (0.10 mmol, 1 equiv), KF (0.24 mmol, 2.4 equiv), [18]crown-6 (0.24 mmol, 2.4 equiv), DME (1 mL). [b] Yield of isolated **2**.

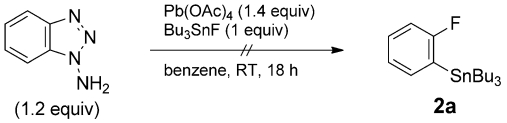
afford the products (**2b** and **2c**) in 78% and 71% yield (Table 2, entries 1 and 2), whereas the reaction of 4,5-difluorobenzyne (from **1d**) or 2,3-naphthalyne (from **1e**) gave a moderate yield (Table 2, entries 3 and 4). Despite the steric congestion around the triple bond, 3,6-dimethoxybenzyne (from **1f**) was smoothly transformed into the respective product (**2f**; Table 2, entry 5). Furthermore, complete regioselectivity was obtained in the reactions of 3-methoxybenzyne (from **1g**), 3-bromobenzyne (from **1h**), and 3-chlorobenzyne (from **1i**); the fluorine atom was incorporated into the *meta* position of the substituents (Table 2, entries 6–8), thus indicating that the fluorine atom acts as a nucleophile in the present reaction.[15] Notably, the trimethylsilyl moiety of 4-(trimethylsilyl)benzyne (from **1j**) remained intact throughout the reaction despite the presence of a fluoride ion, and tributyl[2-fluoro-4-(trimethylsilyl)phenyl]stannane (**2j**) was formed selectively (**2j**/**2′j** = 69:16; Table 2, entry 9).

On the basis of the previous insertion reactions of arynes into σ bonds between a nucleophile and an electrophile,[9,10] a pathway that starts with the formation of zwitterion **3** by nucleophilic attack of the fluorine atom in Bu_3SnF to an aryne may be possible (Scheme 3, path A). The resulting stannyl moiety in **3** then undergoes intramolecular nucleophilic



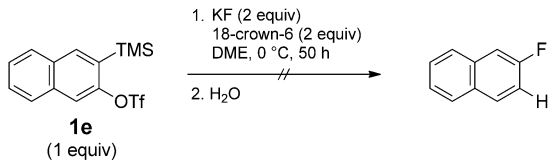
Scheme 3. Plausible pathways for the fluorostannylation.

attack by the aryl anion to give **2**. However, this pathway can be ruled out, because the fluorostannylation product **2a** was not formed at all in the reaction of an aryne generated by oxidation of 1-aminobenzotriazole with $Pb(OAc)_4$,[16] thus implying that the presence of a fluoride ion is required for the fluorostannylation to proceed (Scheme 4). In fact, Bu_3SnF was more soluble in DME in the presence of a fluoride ion,[17] and thus we propose a pathway involving the generation of difluorotributylstannate **4** from Bu_3SnF and a fluoride ion (path B).[18] Subsequent insertion of the aryne into a F–Sn bond via **5**, followed by release of a fluoride ion from **6** provides **2**.[19] Although another pathway, where an aryne interacts stepwise with a fluoride ion and Bu_3SnF via 2-fluoroaryl anion **4** (path C), may also be conceivable,[20] we



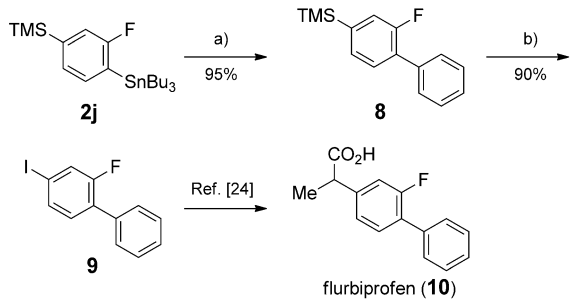
Scheme 4. Reaction of Bu_3SnF with benzyne generated by oxidation.

could not detect the presence of **7** in the reaction of **1e** with a fluoride ion (Scheme 5),[21] thus suggesting that this pathway would not be operative in the present reaction. The regioselectivity in the reaction of 4-(trimethylsilyl)benzyne is ascribable to the electron-donating effect of the trimethylsilyl moiety, thus generation of the aryl anion in **3** is favored at the *para* position (versus *meta*).[22,23]



Scheme 5. Reaction of 2,3-naphthalyne with a fluoride ion.

The synthetic utility of the fluorostannylation products was demonstrated by the formal transformation of **2j** into a pharmacologically significant compound (Scheme 6). A Migita–Kosugi–Stille coupling of **2j** with iodobenzene produced biaryl **8** (95% yield), which then underwent iododesilylation with iodine monochloride to give **9**. Iodobiaryl **9** has been previously converted into anti-inflammatory drug flurbiprofen **10** through palladium-catalyzed carbon–carbon bond-forming reactions.[24]



Scheme 6. Formal total synthesis of flurbiprofen: a) **2j** (1 equiv), iodobenzene (1 equiv), $[Pd(dba)_2]$ (10 mol%), PPh_3 (40 mol%), CuI (75 mol%), DMF, 50°C, 21 h. b) **8** (1 equiv), iodine monochloride (2 equiv), CH_2Cl_2, 0°C, 7 h.

In conclusion, we have demonstrated that direct incorporation of a fluorine atom into aromatic frameworks, together with formation of an Ar–Sn bond can be achieved by the fluorostannylation of arynes; thus providing a convenient and efficient approach to diverse 2-fluorobiaryls of pharmacologically importance. Moreover, the synthetic versatility of the resulting 2-fluoroarylstannanes has been verified by the formal total synthesis of anti-inflammatory drug flurbiprofen. Further studies on Ar–F bond-forming reactions by use of arynes are in progress.

Experimental Section

Typical procedure for the fluorostannylation of arynes: A Schlenk tube equipped with a magnetic stir bar was charged with KF (0.24 mmol) and [18]crown-6 (0.24 mmol). The tube was evacuated at room temperature for 1 h with stirring before addition of DME (1 mL), tributyltin fluoride (0.10 mmol), and **1a** (0.12 mmol) at 0°C under an argon atmosphere. The resulting mixture was stirred at 0°C for 6 h. The mixture was diluted with ethyl acetate and the organic solution was washed three times with brine. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Preparative recycling gel permeation chromatography (eluent: chloroform) gave **2a** as a pale yellow oil (97%).

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[1] T. Furuya, J. E. M. N. Klein, T. Ritter, *Synthesis* **2010**, 1804.
[2] a) T. Hiyama *Organofluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**; b) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218; *Angew. Chem. Int. Ed.* **2005**, *44*, 214; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; e) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501; f) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470.
[3] G. Balz, G. Schiemann, *Ber. Deutsch. Chem. Ges.* **1927**, *60*, 1186.
[4] a) S. D. Kuduk, R. M. DiPardo, M. G. Bock, *Org. Lett.* **2005**, *7*, 577; b) H. Sun, S. G. DiMagno, *Angew. Chem.* **2006**, *118*, 2786; *Angew. Chem. Int. Ed.* **2006**, *45*, 2720; c) H. Sun, S. G. DiMagno, *Chem. Commun.* **2007**, 528.
[5] a) S. Yamada, A. Gavryushin, P. Knochel, *Angew. Chem.* **2010**, *122*, 2261; *Angew. Chem. Int. Ed.* **2010**, *49*, 2215; b) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 2265; *Angew. Chem. Int. Ed.* **2010**, *49*, 2219; c) P. Anbarasan, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 1775.
[6] a) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134; b) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993; c) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060; d) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662; e) N. D. Ball, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 3796; f) X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520; g) T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860; h) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661; i) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard III, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 3793; j) P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150; k) P. Tang, T. Ritter, *Tetrahedron* **2011**, *67*, 4449.
[7] a) H. Hayashi, H. Sonoda, K. Fukumura, T. Nagata, *Chem. Commun.* **2002**, 1618; b) P. Tang, W. Wang, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 11482.
[8] a) M. S. Butler, M. A. Cooper, *J. Antibiot.* **2011**, *64*, 413; b) M. V. Stundick, M. Metz, A. Sampath, J. C. Larsen, *Drug Dev. Res.* **2011**, *72*, 361; c) K. Bush, M. J. Pucci, *Biochem. Pharmacol.* **2011**, *82*, 1528.
[9] For reviews, see: a) D. Peña, D. Pérez, E. Gutián, *Angew. Chem.* **2006**, *118*, 3659; *Angew. Chem. Int. Ed.* **2006**, *45*, 3579; b) H. Yoshida, J. Ohshita, A. Kunai, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199.
[10] a) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem.* **2002**, *114*, 3381; *Angew. Chem. Int. Ed.* **2002**, *41*, 3247; b) H. Yoshida, T. Terayama, J. Ohshita, A. Kunai, *Chem. Commun.* **2004**, 1980; c) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340; d) H. Yoshida, M. Watanabe, J.

Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3292; e) H. Yoshida, T. Minabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3454; f) H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2005**, *46*, 6729; g) H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Chem. Lett.* **2005**, *34*, 1538; h) Z. Liu, R. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 13112; i) H. Yoshida, M. Watanabe, T. Morishita, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 1505; j) H. Yoshida, Y. Mimura, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 2405; k) S. Beltrán-Rodil, D. Peña, E. Guitián, *Synlett* **2007**, 1308; l) H. Yoshida, T. Kishida, M. Watanabe, J. Ohshita, *Chem. Commun.* **2008**, 5963; m) D. G. Pintori, M. F. Greaney, *Org. Lett.* **2010**, *12*, 168; n) H. Yoshida, Y. Ito, Y. Yoshikawa, J. Ohshita, K. Takaki, *Chem. Commun.* **2011**, *47*, 8664.

[11] Arynes are well-known as soft electrophiles. See: S. V. Kessar in *Comprehensive Organic Synthesis Vol. 4* (Eds.: B. M. Trost, I. Flemming), Pergamon, Oxford, **1991**, p. 483.

[12] Although we have also examined an insertion reaction of an aryne into a fluorine–carbonyl σ-bond of an acid fluoride, the desired product was not formed at all in contrast to the results with an acid chloride and bromide. See Ref. [10j].

[13] For insertion reactions of arynes into Sn-containing σ bonds, see: a) H. Yoshida, K. Tanino, J. Ohshita, A. Kunai, *Angew. Chem.* **2004**, *116*, 5162; *Angew. Chem. Int. Ed.* **2004**, *43*, 5052; b) H. Yoshida, K. Tanino, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 5678; c) B. V. Lakshmi, U. K. Wefelscheid, U. Kazmaier, *Synlett* **2011**, 345. See also ref. [10b].

[14] a) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211; b) D. Peña, A. Cobas, D. Pérez, E. Gutián, *Synthesis* **2002**, 1454.

[15] Nucleophilic attack to 3-methoxybenzyne always takes place at the *meta* position to the methoxy group; this can rationally be explained by the inductive electron-withdrawing effect of the methoxy group as well as the steric repulsion. Similarly, 3-bromobenzyne and 3-chlorobenzyne would accept nucleophiles at the *meta* position to the halogen moiety owing to its strong electron-withdrawing effect. For reviews on arynes, see: Refs. [9b] and [11].

[16] C. D. Campbell, C. W. Rees, *J. Chem. Soc. C* **1969**, 742.

[17] Bu_3SnF has proven to be insoluble in DME. See the Supporting Information for details. For insoluble nature of Bu_3SnF, see: a) T. N. Mitchell, K. Kwetkat, B. Godry, *Organometallics* **1991**, *10*, 1633; b) P. D. Lickiss, R. Lucas, *J. Inorg. Organomet. Polym.* **1995**, *5*, 247.

[18] Triorganotin fluorides are apt to form difluorotriorganostannates by action with a fluoride ion, see: a) S. L. Blunden, R. Hill, *J. Organomet. Chem.* **1989**, *371*, 145; b) R. Bujok, M. Makosza, *Synlett* **2004**, 371; c) M. Makosza, R. Bujok, *J. Fluorine Chem.* **2005**, *126*, 209.

[19] Monitoring the reaction by ^{19}F NMR spectroscopy has shown that the fluorostannylation product exists not as **6** but as **2**, even before work-up.

[20] There have been limited examples of the reaction of arynes with a fluoride ion. See: a) A. A. Kolomeitsev, M. Vorobyev, H. Gillandt, *Tetrahedron Lett.* **2008**, *49*, 449; b) V. V. Grushin, W. J. Marshall, *Organometallics* **2008**, *27*, 4825; c) V. Diemer, J. S. Garcia, F. R. Leroux, F. Colobert, *J. Fluorine Chem.* **2012**, *134*, 146.

[21] In addition to this result, the reaction of **1a**, a fluoride ion, and 4-(trifluoromethyl)benzaldehyde did not give 2-fluoro-4′-(trifluoromethyl)benzhydrol at all, thus also suggesting the absence of 2-fluoroaryl anion **4**. See: H. Yoshida, M. Watanabe, H. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2004**, *6*, 4049.

[22] For similar electron-donating effect of a trimethylsilyl moiety in the reaction of 3-(trimethylsilyl)benzyne, see: T. Ikawa, T. Nishiyama, T. Shigeta, S. Mohri, S. Morita, S. Takayanagi, Y. Terauchi, Y. Morikawa, A. Takagi, Y. Ishikawa, S. Fujii, Y. Kita, S. Akai, *Angew. Chem.* **2011**, *123*, 5792; *Angew. Chem. Int. Ed.* **2011**, *50*, 5674.

[23] For the aryne distortion model for understanding regioselectivity, see: a) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G-Y. J. Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267; b) G-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2010**, *132*, 17933; c) S. M. Bronner, J. L. Mackey, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2012**, *134*, 13966.

[24] a) S. Takahashi, M. Uno, K. Seto, S. Mototani (Nitto Chemical Industry Co., Ltd.), Jpn. Kokai Tokkyo Koho JP 62019551, **1987**; b) K. Kobayashi, Y. Yamamoto, N. Miyaura, *Organometallics* **2011**, *30*, 6323.

