ORGANIC LETTERS

2013
Vol. 15, No. 11
2806–2809

Generation of Arynes via Ate Complexes of Arylboronic Esters with an *ortho*-Leaving Group

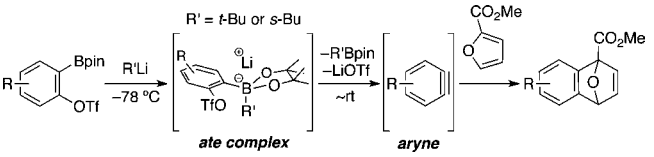
Yuto Sumida, Tomoe Kato, and Takamitsu Hosoya*

Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

thosoya.cb@tmd.ac.jp

Received April 24, 2013

ABSTRACT



An efficient method of generating aryne has been achieved by treating *ortho*-(trifluoromethanesulfonyloxy)arylboronic acid pinacol ester with *tert*- or *sec*-butyllithium. Monitoring the reaction by ^{11}B NMR has indicated that a boron-ate complex formed in situ is the eventual precursor that converts into aryne near room temperature. The prior formation of the ate complex at a low temperature has enabled us to use various arynophiles, including those bearing base-sensitive groups. The ready availability of the aryne precursors and mutual orthogonality in aryne generation with widely used *ortho*-silylaryl triflate have enhanced the utility of the method.

Aryne is a highly reactive species that has been attracting much attention because of its intriguing structure and properties.[1] Various methods of aryne generation have been developed so far, enabling the straightforward construction of diverse aromatic molecules,[2,3] with successful application to a number of total syntheses of complex natural products.[4] Aryne is most simply generated by eliminating two adjacent substituents on an arene ring, with one substituent usually being an aryl anion equivalent and the other being a leaving group.[5] Decarboxylative denitrogenation of *ortho*-arene-diazonium carboxylate,[5a,b] fluoride-mediated activation of *ortho*-silylaryl triflate,[5f] and halogen−lithium exchange of *ortho*-haloaryl triflate[5g] are typical examples. Herein we disclose that aryne can also be efficiently generated from an ate complex of an arylboronic ester that has a good leaving group at the *ortho*-position.

Pioneering work on aryne generation from *ortho*-haloarylboronic acid had been reported half a century ago: treatment of 2-chlorophenylboronic acid in ether with *n*-butyllithium (3 equiv) in the presence of furan at rt,

(1) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Gilchrist, T. L. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 11. (c) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 2.3. (d) Hart, H. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1994; Chapter 18.

(2) For some recent reviews on arynes, see: (a) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579–3581. (b) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291. (c) Wentrup, C. *Aust. J. Chem.* **2010**, *63*, 979–986. (d) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987–1001. (e) Yoshida, H.; Takaki, K. *Heterocycles* **2012**, *85*, 1333–1349. (f) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725–1732. (g) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520–1522. (h) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140–3152. (i) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116–125. (j) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191–218. (k) Hoffmann, R. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2655–2656.

(3) For some recent aryne chemistries, see: (a) Cant, A. A.; Bertrand, G. H.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199–5202. (b) Ikawa, T.; Takagi, A.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Kakiguchi, K.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5563–5566. (c) Smith, A. B., III.; Kim, W.-S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787–6792. (d) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488–4491. (e) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5674–5677. (f) Hamura, T.; Chuda, Y.; Nakatsuji, Y.; Suzuki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3368–3372. (g) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966–13969. (h) Candito, D. A.; Dobrovolsky, D.; Lautens, M. *J. Am. Chem. Soc.* **2012**, *134*, 15572–15580. (i) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54–60.

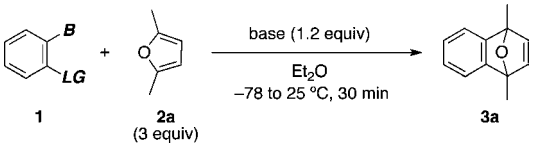
(4) (a) For recent reviews on the synthesis of natural products via arynes, see: Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766–3778. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577.

10.1021/ol401140d
Published on Web 05/21/2013

followed by acidic workup, afforded 1-naphthol, a cycloadduct derivative, in 55−60% yield.[6,7] While the boron-ate complex, assumed to be formed in situ, was proposed as the benzyne precursor in this report, no direct evidence was shown, and to the best of our knowledge, the substrate scopes have not been explored at all since. We presumed that the scope of this type of reaction could be greatly expanded by optimizing the reaction conditions. After extensive screening of the conditions using 2,5-dimethylfuran (**2a**) as an arynophile, we succeeded in finding a suitable combination of benzyne precursor, base, and solvent (Table 1): the desired cycloadduct **3a** was obtained in an excellent yield by adding *tert*-butyllithium (1.2 equiv) to 2-(trifluoromethanesulfonyloxy)arylboronic acid pinacol ester (**1a**) in ether at −78 °C in the presence of an excess of **2a** (3 equiv) and then warming the mixture to 25 °C (entry 1). Performing the reaction in THF instead of ether led to a slightly lower yield of **3a** (entry 2). Using *sec*-butyllithium as the base also gave a satisfactory result (entry 3), working better than *tert*-butyllithium for some substrates (vide infra). However, *n*-butyllithium gave **3a** in a poor yield, also providing a phenolic byproduct that presumably arose from the nucleophilic cleavage of the triflate moiety of **1a** (entry 4). All of the other bases examined, including strong bases such as phenyllithium and *tert*-butylmagnesium chloride, as well as milder bases such as potassium *tert*-butoxide, cesium carbonate, and tetrabutylammonium fluoride (1.0 M in THF), were totally ineffective (entries 5−9). Changing the leaving group of **1a** to methanesulfonyloxy considerably diminished the reaction efficiency (entry 10), whereas altering it to *p*-toluenesulfonyloxy, bromo, or chloro gave the desired product in moderate yields (entries 11−13). Neopentyl glycol ester **1f** also served as a reasonable precursor in combination with *sec*-butyllithium (entries 14 and 15), but nonesterified phenylboronic acids did not, regardless of the type of leaving groups employed (entries 16 and 17).

The intermediacy of a boron-ate complex in this reaction was strongly suggested by the NMR study. The reaction of **1a** and **2a** (1.4 equiv) carried out in THF-d_8 was continuously monitored by ^{1}H, ^{11}B, and ^{19}F NMR at various temperatures, before and after the addition of *tert*-butyllithium (1.2 equiv). A set of ^{11}B NMR spectra are shown in Figure 1.[8] By the addition of *tert*-butyllithium to the

Table 1. Optimization of the Reaction Conditions



entry	B^a	*LG*	**1**	base	yield (%)^b
1	Bpin	OTf	**1a**	*t*-BuLi	97 (95)^c
2^d	Bpin	OTf	**1a**	*t*-BuLi	76
3	Bpin	OTf	**1a**	*s*-BuLi	89
4	Bpin	OTf	**1a**	*n*-BuLi	27
5	Bpin	OTf	**1a**	PhLi	15
6	Bpin	OTf	**1a**	*t*-BuMgCl	<1
7	Bpin	OTf	**1a**	*t*-BuOK	11
8^e	Bpin	OTf	**1a**	Cs_2CO_3	12
9^e	Bpin	OTf	**1a**	*n*-Bu_4NF	0
10^e	Bpin	OMs	**1b**	*t*-BuLi	3
11	Bpin	OTs	**1c**	*t*-BuLi	64
12	Bpin	Br	**1d**	*t*-BuLi	54
13	Bpin	Cl	**1e**	*t*-BuLi	68
14	Bnpg	OTf	**1f**	*t*-BuLi	58
15	Bnpg	OTf	**1f**	*s*-BuLi	73
16^f	$B(OH)_2$	OTf	**1g**	*n*-BuLi	18
17^f	$B(OH)_2$	Cl	**1h**	*n*-BuLi	40

^{a} pin = pinacol; npg = neopentyl glycol. ^{b} Determined by ^{1}H NMR unless otherwise noted. ^{c} Isolated yield in parentheses. ^{d} THF was used as a solvent instead of Et_2O. ^{e} Base was added at 0 °C, and the reaction was then warmed up to 25 °C. ^{f} 3.6 equiv of *n*-butyllithium was used.

mixture at 240 K, the signal for **1a** (δ 27.8 ppm) completely disappeared and, instead, a new peak (δ 5.8 ppm) with a comparable chemical shift to the analogous boron-ate complexes appeared.[9] This peak gradually disappeared with increasing the temperature to 300 K, accompanied by the emergence of another peak (δ 32.7 ppm), which was identical to *t*-BuBpin, separately prepared,[10] showing the progression of the reaction. A similar tendency was observed in the ^{1}H and ^{19}F NMR studies.[8] These results strongly indicate that the boron-ate complex **4** formed in situ is the eventual benzyne precursor, which is stable in the solution below 0 °C, but breaks down into benzyne, *t*-BuBpin, and LiOTf near rt.

The optimized conditions were generally applicable to various arynophiles showing a broad substrate scope for the method (Table 2). Although the use of a strong base was required for this reaction, we found that arynophiles bearing base-sensitive groups could also be used by adding them after the boron-ate complex was formed, at the time

(5) For representative aryne precursors and generation methods, see: (a) Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, *82*, 3802. (b) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549. (c) Wittig, G.; Hoffmann, R. W. *Org. Synth.* **1967**, *47*, 4. (d) Campbell, C. D.; Rees, C. W. *J. Chem. Soc., C* **1969**, 742–747. (e) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, *48*, 12. (f) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214. (g) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736. (h) Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983–984. (i) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364–4366. (j) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208–212.

(6) Cainelli, G.; Zubiani, G.; Morrocchi, S. *Chim. Ind. (Milan, Italy)* **1964**, *46*, 1489–1490.

(7) For preparation of benzyne−nickel(0) and −palladium(0) complexes from *ortho*-bromophenylboronic acid pinacol ester, see: Retbøll, M.; Edwards, A. J.; Rae, A. D.; Willis, A. C.; Bennett, M. A.; Wenger, E. *J. Am. Chem. Soc.* **2002**, *124*, 8348–8360.

(8) See Supporting Information for ^{1}H and ^{19}F NMR spectra.

(9) (a) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674–10676. (b) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098. (c) Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316–5319.

(10) *t*-BuBpin was prepared according to: Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602–9610.

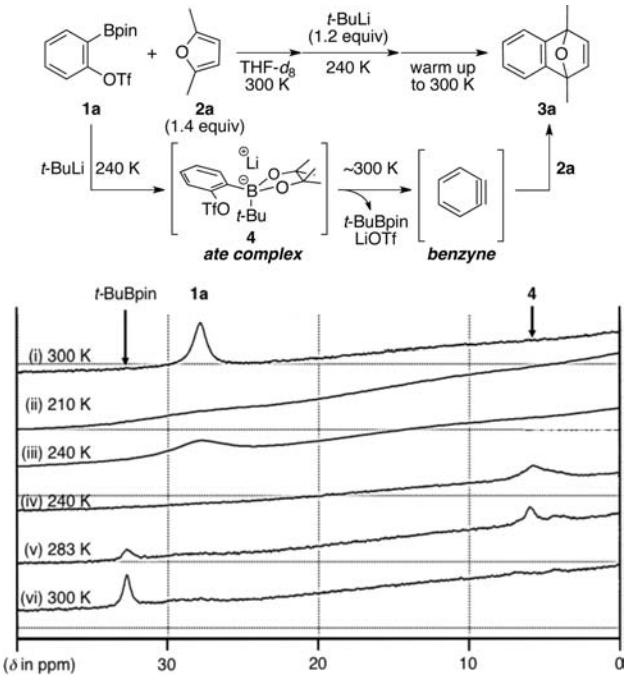
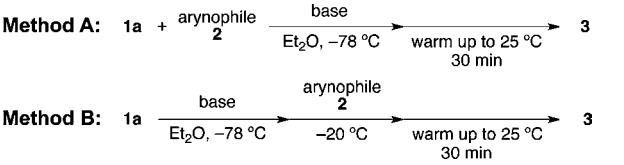


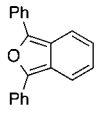
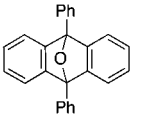
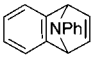
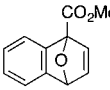
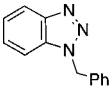
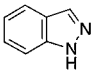
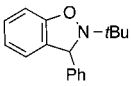
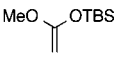
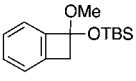
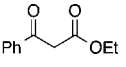
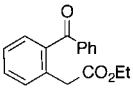
Figure 1. ^{11}B NMR spectra (193 MHz) measured during the reaction of **1a** and **2a** (1.4 equiv) in THF-d_8: (i) the signal for **1a** (δ 27.8 ppm) was observed at 300 K; (ii) no distinct signal could be observed when the temperature was decreased to 210 K; (iii) a broad peak for **1a** reappeared at 240 K; (iv) by adding *t*-BuLi at 240 K, the signal for **1a** disappeared and a new peak regarded as the boron-ate complex **4** (δ 5.8 ppm) appeared; (v) by increasing the temperature to 283 K, a new peak identical to *t*-BuBpin (δ 32.7 ppm) gradually appeared; (vi) the signals converged in a single peak at 300 K.

when no free base exists in the reaction mixture (Method B). Using either of the methods, with slight modifications as needed, benzyne generated from **1a** smoothly reacted with various arynophiles, including dienes **2b**–**2d** (entries 1–3), 1,3-dipolar compounds **2e**–**2g** (entries 4–6), and ketene silyl acetal **2h** (entry 7), to give corresponding cycloadducts **3b**–**3h** efficiently. Notably, the reaction could be uneventfully performed in gram-scale as demonstrated in the reaction with **2d** (entry 3). In addition, the reaction with β-ketoester **2i** was remarkably improved by the combined use of cesium fluoride, by which the enolization of **2i** was facilitated, affording the formally benzyne-inserted product **3i** in high yield (entry 8).

The ready synthetic accessibility to aryne precursors further enhanced the utility of the method. The key intermediate, *ortho*-hydroxyarylboronic acid, could be smoothly prepared using conventional methods such as treating *ortho*-lithiated phenols with trialkyl borate and Pd-catalyzed Miyaura

Table 2. Scope of Arynophiles



entry	arynophile		method	base	product		yield (%)[a]
1[b]		**2b**	**A**	*t*-BuLi		**3b**	quant
2[c]		**2c**	**A**	*s*-BuLi		**3c**	69
3[d,e]		**2d**	**B**	*s*-BuLi		**3d**	88 (77)[f]
4[c]		**2e**	**A**	*s*-BuLi		**3e**	92
5[c]		**2f**	**B**	*s*-BuLi		**3f**	66 (3)[f]
6[d]		**2g**	**B**	*s*-BuLi		**3g**	96 (25)[f]
7[d]		**2h**	**B**	*s*-BuLi		**3h**	71
8[d]		**2i**	**B**[g]	*s*-BuLi CsF		**3i**	87

[a] Isolated yields. [b] Molar ratio: **1a**/arynophile/base = 1.2/1.0/1.4. [c] Molar ratio: **1a**/arynophile/base = 1.0/3.0/1.1–1.2. [d] Molar ratio: **1a**/arynophile/base = 1.2–1.5/1.0/1.2–1.5. [e] 5.0 mmol of **2d** were used. [f] Yields of the products obtained from the reactions performed with method A determined by ^{1}H NMR in parentheses. [g] A solution prepared from **1a** and *s*-BuLi was added to a separately prepared mixture of **2i** and CsF (1.0 equiv).

borylation of *ortho*-halophenols.[11] Furthermore, Ir-catalyzed direct *ortho*-borylation of phenols, reported by Hartwig and co-workers,[12] particularly suited our purpose as clearly demonstrated in the short-step syntheses of some *ortho*-borylaryl triflates prepared from phenols **5a**–**5c**. Based on this strategy, regioisomers of an indazole-type steroid analog, **3l** and **3l′**, could be easily prepared from β-estradiol derivative **5c** (Figure 2).[13]

Some notable results were obtained from experiments performed to compare the reactivities of *ortho*-borylaryl triflate and *ortho*-silylaryl triflate, which is one of the most widely used aryne precursors. The reaction of aryl triflate **1m**,[3b] having both boryl and silyl groups at each *ortho*-position, with **2a** using *sec*-butyllithium afforded the expected silyl-containing product **3m** exclusively in 81%

(11) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.

(12) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (c) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

(13) See Supporting Information for details.

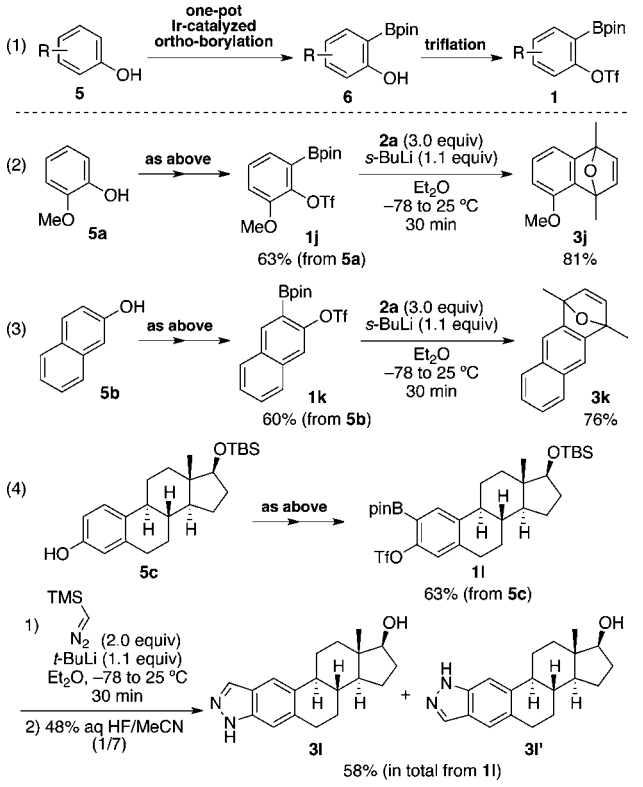
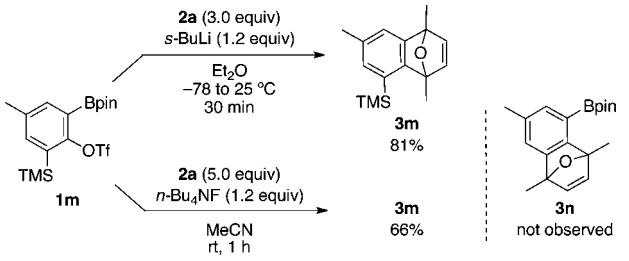


Figure 2. Preparation of aryne precursors by Ir-catalyzed direct *ortho*-borylation of phenols followed by triflation and their applications.

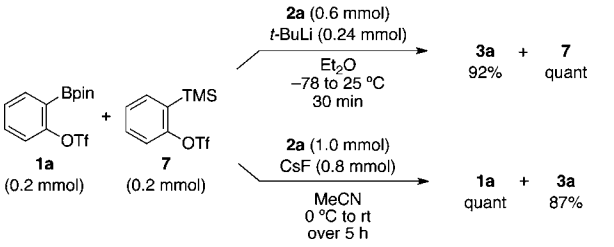
yield (Scheme 1). Moreover, treatment with tetrabutylammonium fluoride (1.0 M in THF) at rt also provided **3m** without any of the other possible boron-containing compound **3n** being found, showing good agreement with the result previously mentioned by Akai and co-workers.[3b] Although this result could be attributed to the nature of boron being more fluorophilic than silicon, we also observed that the borylaryl triflates **1a** and **1j** could not react under the same fluoride-activating conditions, indicating that the ability of **1m** to generate 3-silylaryne was greatly enhanced by the trimethylsilyl group. Based on these results, an orthogonal relationship between *ortho*-borylphenyl triflate **1a** and *ortho*-silylphenyl triflate **7** in benzyne generation was clearly demonstrated in competitive reactions with **2a** under the appropriate conditions for each precursor (Scheme 2). The reaction performed by adding *tert*-butyllithium to the mixture resulted in the complete consumption of **1a** with quantitative recovery of **7**. In contrast, fluoride could mediate the benzyne generation only from **7**, leaving **1a** apparently intact, indicating that elimination took place more rapidly from silicate than from the boron-ate complex. These results suggest that, in principle, the back-to-back generation of arynes, in any order, would be possible using a substrate that has both *ortho*-borylaryl triflate and *ortho*-silylaryl triflate substructures.[14]

(14) For sequential generation of arynes from the 1,4-benzdiyne precursor, see: (a) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842–6844. (b) Arisawa, T.; Hamura, T.; Uekusa, H.; Matsumoto, T.; Suzuki, K. *Synlett* **2008**, 1179–1184.

Scheme 1. Selective Generation of 3-Silylaryne from 2-Boryl-6-silyl-4-tolyl triflate **1m** under either Base- or Fluoride-Activating Conditions



Scheme 2. Mutual Orthogonality in Benzyne Generation between *ortho*-Borylphenyl Triflate and *ortho*-Silylphenyl Triflate[a]



[a] Yields determined by ^{1}H NMR.

In summary, we have demonstrated that arynes could be efficiently generated near rt from ate complexes of arylboronic esters bearing an *ortho*-OTf group. The prior formation of the boron-ate complex by adding *tert*- or *sec*-butyllithium to the ester at a low temperature allowed us to use arynophiles that have functional groups susceptible to strong bases, greatly expanding the scope of the method. The utility of the method was also enhanced by the ready availability of the *ortho*-borylaryl triflate and mutual orthogonality in aryne generation with widely used *ortho*-silylaryl triflate, which will enable the facile construction of structurally complex polysubstituted arenes.

Acknowledgment. The authors thank Mr. Natsuhiko Sugimura (Materials Characterization Central Laboratory) and Dr. Takashi Niwa at Waseda University for ^{11}B NMR analyses, Dr. Hiroyuki Masuno and Ms. Ayako Hosoya at Tokyo Medical and Dental University for HRMS analyses, and Central Glass Co., Ltd. for a generous gift of Tf_2O. This work was partially supported by Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT, Japan.

Supporting Information Available. Experimental procedures and characterization data, including copies of NMR spectra, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.