

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

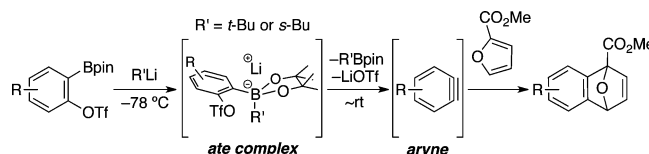
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ABSTRACT



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,

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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 ¹H, ¹¹B, and ¹⁹F NMR at various temperatures, before and after the addition of *tert*-butyllithium (1.2 equiv). A set of ¹¹B 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	<i>t</i> -BuLi	97 (95) ^c
2 ^d	Bpin	OTf	1a	<i>t</i> -BuLi	76
3	Bpin	OTf	1a	<i>s</i> -BuLi	89
4	Bpin	OTf	1a	<i>n</i> -BuLi	27
5	Bpin	OTf	1a	PhLi	15
6	Bpin	OTf	1a	<i>t</i> -BuMgCl	<1
7	Bpin	OTf	1a	<i>t</i> -BuOK	11
8 ^e	Bpin	OTf	1a	Cs ₂ CO ₃	12
9 ^e	Bpin	OTf	1a	<i>n</i> -Bu ₄ NF	0
10 ^e	Bpin	OMs	1b	<i>t</i> -BuLi	3
11	Bpin	OTs	1c	<i>t</i> -BuLi	64
12	Bpin	Br	1d	<i>t</i> -BuLi	54
13	Bpin	Cl	1e	<i>t</i> -BuLi	68
14	Bnpg	OTf	1f	<i>t</i> -BuLi	58
15	Bnpg	OTf	1f	<i>s</i> -BuLi	73
16 ^f	B(OH) ₂	OTf	1g	<i>n</i> -BuLi	18
17 ^f	B(OH) ₂	Cl	1h	<i>n</i> -BuLi	40

^a pin = pinacol; npg = neopentyl glycol. ^b Determined by ¹H NMR unless otherwise noted. ^c Isolated yield in parentheses. ^d THF was used as a solvent instead of Et₂O. ^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 ¹H and ¹⁹F 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

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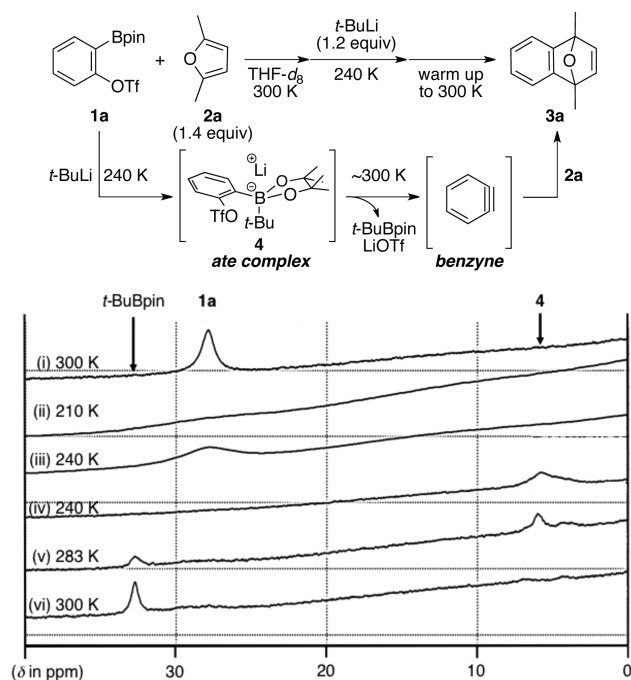
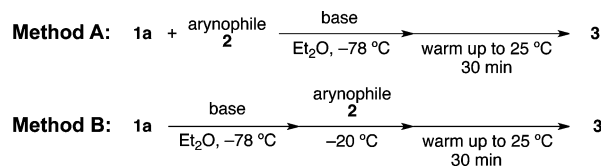


Figure 1. ^{11}B NMR spectra (193 MHz) measured during the reaction of **1a** and **2a** (1.4 equiv) in $\text{THF-}d_8$: (i) the signal for **1a** (δ 27.8 ppm) was observed at 300 K; (ii) no distinct signal could be observed when the temperature was decreased to 210 K; (iii) a broad peak for **1a** 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 aryneophiles, 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 Aryneophiles



entry	aryneophile	method	base	product	yield (%) ^a
1 ^b		A	<i>t</i> -BuLi		quant
2 ^c		A	<i>s</i> -BuLi		69
3 ^{d,e}		B	<i>s</i> -BuLi		88 (77) ^f
4 ^c		A	<i>s</i> -BuLi		92
5 ^c		B	<i>s</i> -BuLi		66 (3) ^f
6 ^d		B	<i>s</i> -BuLi		96 (25) ^f
7 ^d		B	<i>s</i> -BuLi		71
8 ^d		B ^g	<i>s</i> -BuLi CsF		87

^a Isolated yields. ^b Molar ratio: **1a**/aryneophile/base = 1.2/1.0/1.4. ^c Molar ratio: **1a**/aryneophile/base = 1.0/3.0/1.1–1.2. ^d Molar ratio: **1a**/aryneophile/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 ^1H 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, **3i** and **3i'**, 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%

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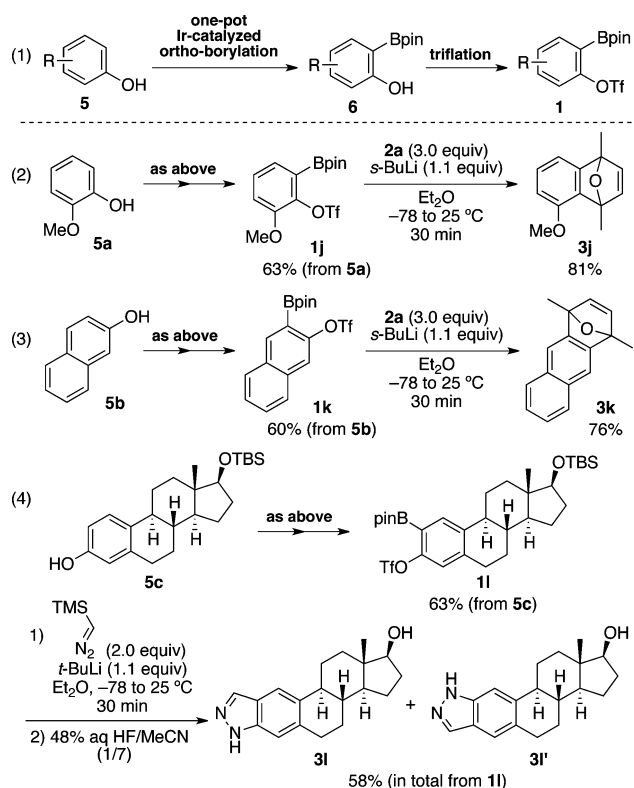
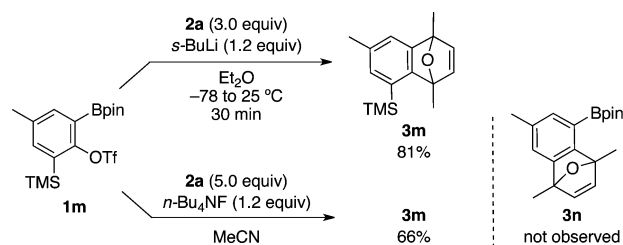


Figure 2. Preparation of aryne precursors by Ir-catalyzed direct *ortho*-borylation of phenols followed by triflation and their applications.

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

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



^a Yields determined by ¹H NMR.

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

In summary, we have demonstrated that arynes could be efficiently generated near rt from ate complexes of aryl-boronic 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.

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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.