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Reductive stereo- and regiocontrolled boryllithiation and borylsodiation of arylacetylenes using flow microreactors

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Given their prevalence within valuable organic compounds, constructing multisubstituted alkenes while stereo- and regiochemically controlling the substituents on the alkene stands as a pivotal objective in organic synthesis. Now, the stereo- and regioselective *syn*-boryllithiation and *syn*-borylsodiation of arylacetylenes have been achieved by reductive borylmetallation using flow microreactors. This method involves the fast mixing of a solution of an alkyne and stoichiometric alkoxypinacolborane with an alkali metal arenide solution, which efficiently generates highly reactive β-borylalkenyllithium and β-borylalkenylsodium species by suppressing the undesired diboration that inevitably occurs in a batch reactor. Unlike conventional three-component borofunctionalization, the intermediates can be generated in the absence of electrophiles, which has enabled diverse electrophiles to participate in various *syn*-borofunctionalizations such as borylsilylation, borylhalogenation, borylcarbonylation, borylsulfenylation and borylarylation. Trapping with aldehydes and ketones provides a series of oxaboroles of biological interest. Furthermore, unsymmetric diarylacetylenes undergo highly regioselective borylmetallation, which is applicable to the stereo- and regiocontrolled syntheses of multisubstituted oxaboroles and differently tetrasubstituted alkenes.

Multisubstituted alkenes play a significant role in various fields such as pharmaceuticals[1–4] and materials science[5–7] due to their diverse functional group arrangements. The stereo- and regioselective synthesis of multisubstituted alkenes is a crucial aspect of organic chemistry[8–10] because it allows the synthesis of specific isomers with distinct physical and chemical properties including bioactivities[11]. Hence, the development of efficient methods for the stereo- and regiocontrolled synthesis of multisubstituted alkenes is essential in modern organic chemistry because existing methods, such as the alkenation reactions of carbonyl compounds (including Wittig and Mukaiyama–McMurry reactions) and alkene metathesis, usually result in only moderate stereoselectivity (Fig. 1a)[12–15].

The addition of metal/metalloid species onto alkynes, catalysed by transition metals, proceeds with high *syn* stereoselectivity and provides alkenylmetal/metalloid adducts as useful synthetic intermediates for stereodefined multisubstituted alkenes[16–18]. Among such *syn*-addition reactions, borofunctionalization of alkynes is a powerful and practical tool for the simultaneous installation of a convertible boryl group and a functional group to alkynes[19–21]. The catalytic borofunctionalization often employs bimetallic reagents B–FG (FG = functional group) such as silylborane and stannylborane, and the addition products are very useful building blocks due to their stability, high functional group tolerance, and versatility of transformations (Fig. 1b)[22–24]. However, a limited variety of the reagents can undergo oxidative addition to a

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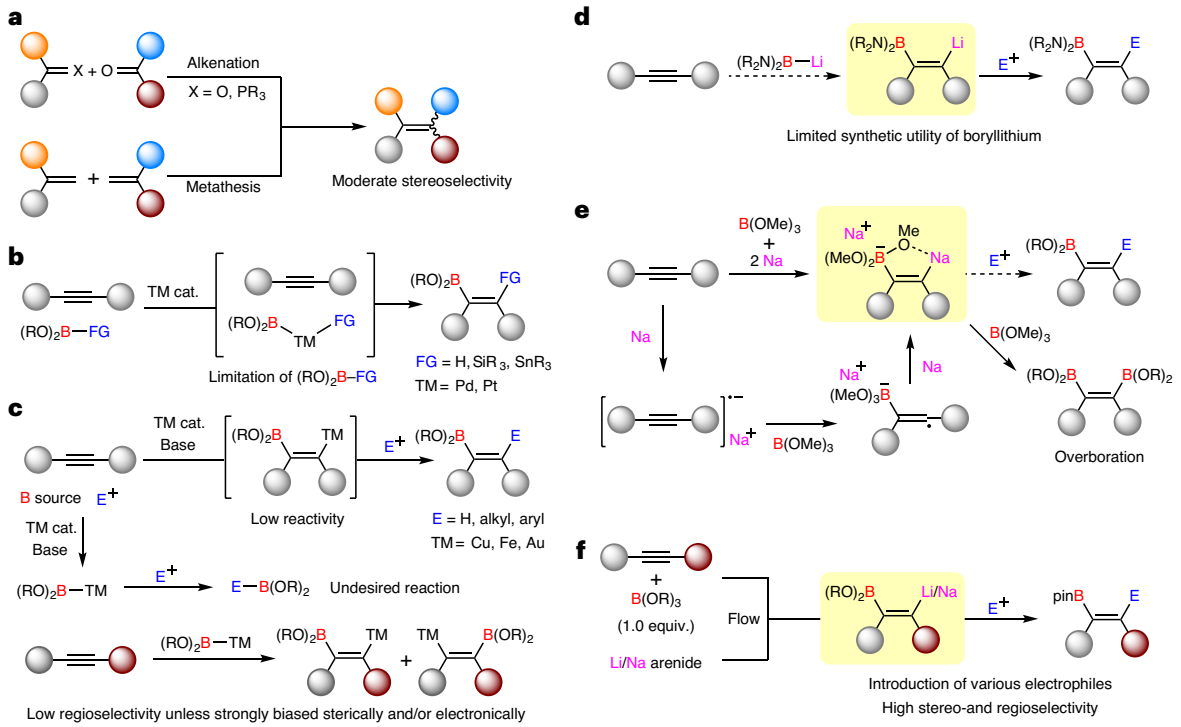


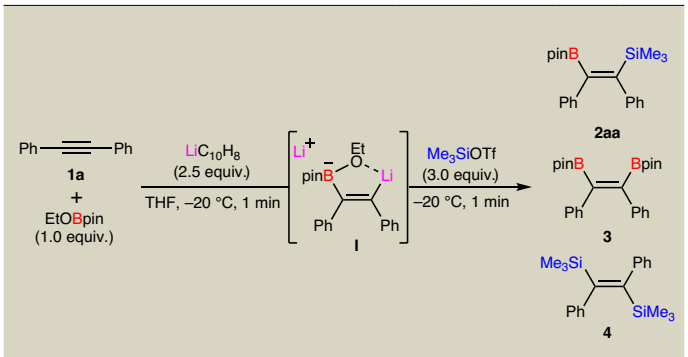
Fig. 1 | Approaches to multisubstituted alkenes. a, Synthesis of multisubstituted alkenes by alkenation of carbonyls and alkene metathesis often result in moderate stereoselectivity[12–15]. **b**, Stereoselective two-component borofunctionalization of alkynes has limited reagents B–FG that undergo oxidative addition[22–24]. **c**, Stereoselective three-component borofunctionalization of alkynes often results in undesired side reactions and limited reactivity of the generated β-alkenylmetal species, which restricts the electrophile scope. Regioselectivity of the addition to alkynes is difficult to control unless they are highly unsymmetric sterically and/or electronically[21,25–28]. **d**, An 'additive' approach using boryllithiums is theoretically ideal but difficult to handle practically[29,30]. **e**, A 'reductive' approach using an alkali metal and alkoxyborane cannot effectively control the highly reactive *syn*-β-borylalkenylmetals for borofunctionalizations[31–33]. **f**, This study focuses on the efficient generation of *syn*-β-borylalkenyl alkali metal intermediates using flow microreactors, followed by the reactions with various electrophiles to achieve a broad range of stereo- and regioselective borofunctionalizations. TM, transition metal; E, electrophile.

transition metal centre, restricting substituents that can be introduced in atom- and step-economical manners.

In the past decade, three-component borofunctionalization, in which a boron source and an electrophile are individually employed, has been greatly developed, most frequently under copper catalysis (Fig. 1c)[21,25–28]. A borylcopper species is first formed from a boron source such as B_2pin_2 (pin = pinacolato) via σ-bond metathesis. The subsequent *syn* addition of the borylcopper species to an alkyne affords a β-borylalkenylcopper intermediate, which is trapped by a coexisting electrophile to stereoselectively give the corresponding multisubstituted alkenylboron compound. The three-component borofunctionalization has enabled the direct introduction of alkyl substituents, which is difficult via conventional two-component borofunctionalization. However, the useful three-component borofunctionalization still has some intrinsic drawbacks. First, the addition of boryl metal species to alkynes competes with nucleophilic attack on coexisting electrophiles, requiring extensive investigation to find appropriate electrophiles and reaction conditions for each desired functionalization. Second, versatilely reactive alkenylmetal species such as alkenyllithiums cannot be generated as intermediates. These two issues pose significant limitations to the electrophiles for the three-component borofunctionalization. The final issue concerns regioselectivity, which is true of all addition reactions: addition of borylmetals onto alkynes is regioselective only when the alkynes are strongly biased sterically and/or electronically.

It has been thus envisioned that the generation of reactive β-borylalkenylmetal species from alkynes in the absence of electrophiles would make it possible to introduce electrophiles without the competing nucleophilic attack on electrophiles and to expand the electrophile scope. Although boryllithium species[29,30] are ideal as borylmetallating reagents, their lack of stability, diversity and accessibility has prevented synthetic organic chemists from synthesizing, using and investigating them for organic synthesis (Fig. 1d).

Table 1 | Reductive borylsilylation using batch reactors



Addition method	NMR spectroscopic yield (%)[a]			
	1a	2aa	3	4
A solution of $LiC_{10}H_8$ was added to a solution of **1a** and EtOBpin	10	14	6	12
A solution of **1a** and EtOBpin was added to a solution of $LiC_{10}H_8$	9	27	11	4

[a]Yields were determined by ^{1}H NMR spectroscopic analysis using mesitylene as an internal standard.

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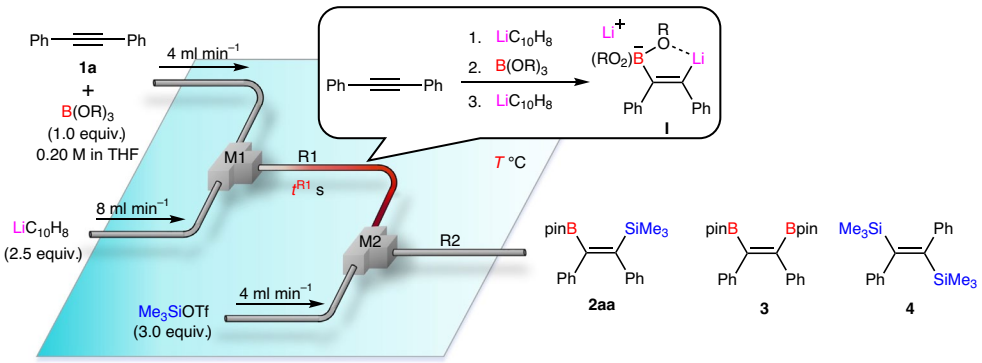
Table 2 | Optimization of reductive borylmetallation/silylation using flow microreactors



Entry	$B(OR)_3$	T (°C)	Total flow rate at M1 (ml min^{-1})	t^{R1} (s)	NMR spectroscopic yield (%)[b]			
					1a	2aa	3	4
1[a]	$B(OMe)_3$	0	12	0.14	0	15	0	9
2[a]	$B(O^iPr)_3$	0	12	0.14	0	12	0	22
3	MeOBpin	0	12	0.14	0	60	Trace	5
4	EtOBpin	0	12	0.14	0	72	Trace	4
5	^{i}PrOBpin	0	12	0.14	0	68	0	3
6	EtOBpin	−20	12	0.14	0	84	Trace	3
7	EtOBpin	−40	12	0.14	0	64	0	2
8	EtOBpin	−78	12	0.14	7	29	0	38
9	EtOBpin	−20	12	1.96	0	75	1	2
10	EtOBpin	−20	12	7.86	0	73	Trace	2
11	EtOBpin	−20	12	39.3	0	66	1	1
12	EtOBpin	−20	3	0.14	35	34	1	4
13	EtOBpin	−20	0.75	0.14	42	14	2	2

[a]The resulting solution was treated with pinacol (1.5 equiv.). [b]Yields were determined by ^{1}H NMR spectroscopic analysis using mesitylene as an internal standard.

In addition to conventional 'additive' approaches (Fig. 1b–d), we have been investigating 'reductive' approaches for difunctionalizations of alkynes[31–33]. Among these, we envisioned that the reductive diboration of alkynes[32] would provide a clue to the development of excellent borylmetallation (Fig. 1e). The reductive process begins with the single-electron reduction of alkyne by sodium metal to generate the radical anion of the alkyne, which is rapidly trapped by a boron electrophile. The subsequent single-electron reduction would form *syn*-β-borylalkenylsodium intermediates with the sodium atom coordinated intramolecularly by a methoxy group. Although the intermediates are ideal for borofunctionalizations, they uncontrollably react rapidly with the remaining boron electrophile to give the diborated product, even when only a stoichiometric amount of the boron electrophile is used.

Here we disclose a method to generate and use versatile *syn*-β-borylalkenyl alkali metal intermediates in a controlled manner for the stereo- and regioselective synthesis of multisubstituted alkenes. This method utilizes the fast mixing of alkynes with a single-electron reductant in the presence of stoichiometric alkoxypinacolborane using flow microreactors, which suppresses undesired diboration and yields reactive *syn*-β-borylalkenyllithium and *syn*-β-borylalkenylsodium species with high efficiency (Fig. 1f). The generation of the versatile intermediates is followed by the reactions with various electrophiles to achieve a wide range of borofunctionalizations. Furthermore, the reductive borylmetallation of unsymmetric alkynes was found to proceed with exceptionally high regioselectivity. Our findings will have promising applications in the efficient and stereo/regiocontrolled syntheses of multisubstituted alkenes of interest.

Results and discussion

Optimization of reductive boryllithiation

Apart from the result summarized briefly in Fig. 1e, our attempts at reductive borylmetallation of diphenylacetylene (**1a**) followed by electrophilic silylation with chlorotrimethylsilane in a batch reactor were unsuccessful, as shown in Table 1. Lithium naphthalenide ($LiC_{10}H_8$) was used as a homogeneous reductant for more rapid single-electron reduction. In a conventional batch reactor, a solution of $LiC_{10}H_8$ was added to a solution of equimolar amounts of **1a** and EtOBpin. One minute later, the resulting solution was treated with trimethylsilyl triflate to trap a boryllithiated intermediate. However, the desired borylsilylated product **2aa** was obtained in only low yields, along with side products **3** and **4**. Side product **3** was formed via the reaction of the boryllithiated intermediate with the remaining adjacent EtOBpin to wastefully consume EtOBpin (Fig. 1e). Side product **4** is believed to be formed from the reaction of **1a** with Me_3SiOTf using $LiC_{10}H_8$, indicating the presence of unreacted **1a** when Me_3SiOTf was added to the mixture. The yield and selectivity of **2aa** did not improve even when the addition order was reversed.

After analysing the results in Table 1, we concluded that low mixing efficiency may have caused unwanted competition between the reduction of **1a** with $LiC_{10}H_8$ and borylation of the boryllithiated intermediate with EtOBpin. Recently, flow microreactors[34–38] have gained significant attention for controlling fast competitive reactions[39–41]. Whereas it generally takes a few seconds for two components to mix thoroughly in a batch reactor[42], flow microreactors enable fast mixing by colliding two solutions in a microscopic space. This ensures that the

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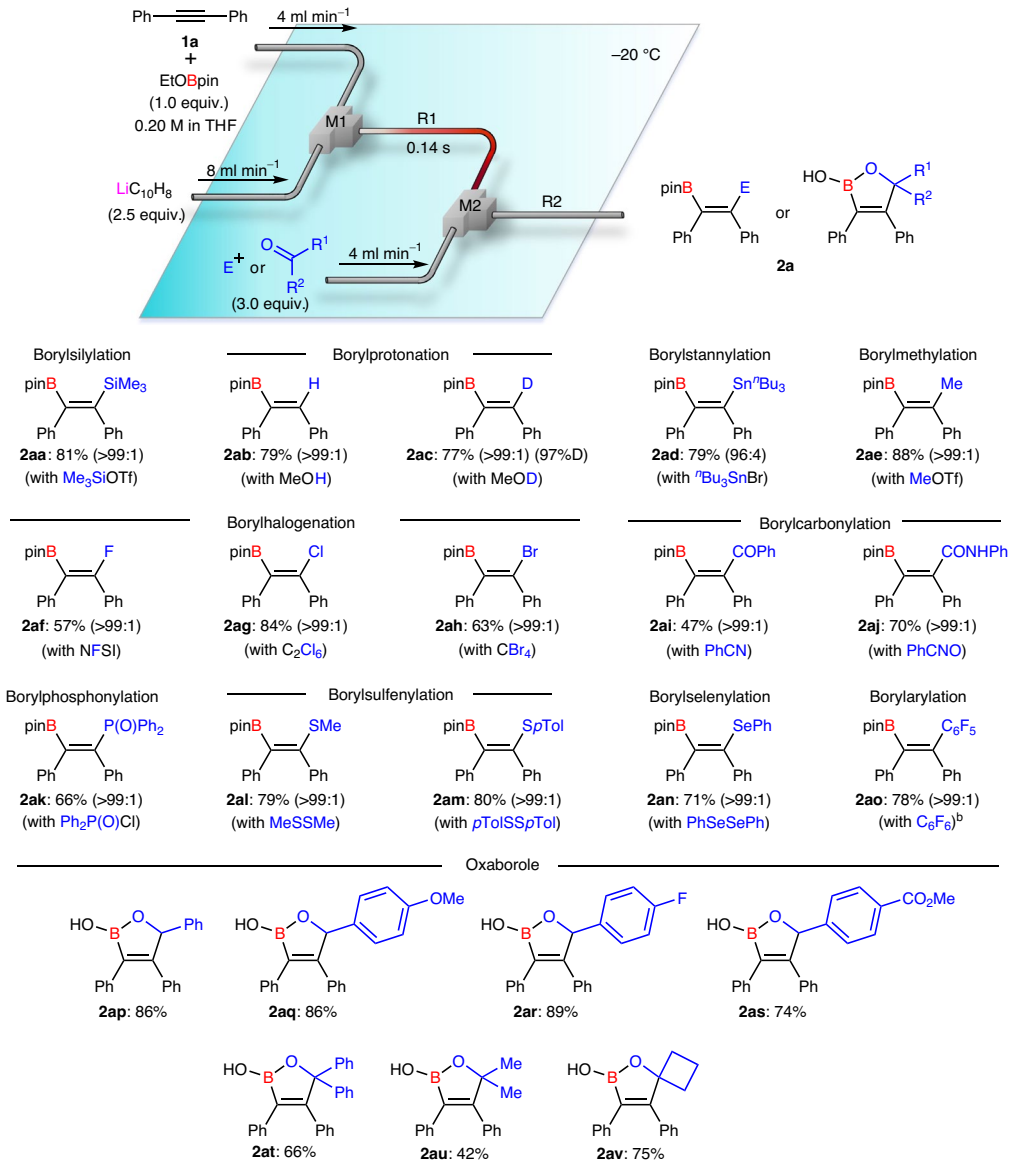
Table 3 | Scope with respect to the second electrophile[a]



[a]Isolated yields are shown. Ratios of the mode of addition *syn*:*anti* are in parentheses. [b]$NaC_{10}H_8$ was used instead of $LiC_{10}H_8$. NFSI, *N*-fluorobenzenesulfonimide; *p*Tol, *p*-tolyl.

reaction proceeds according to the intrinsic reaction rate. Therefore, we envisaged that fast mixing of an alkyne with an alkali metal arenide would enable the rapid generation of the corresponding radical anion of alkyne, consuming all the alkoxyborane instantaneously and avoiding the undesired diboration.

A flow system with two micromixers (**M1, M2**) and two microtube reactors (**R1, R2**) was designed to optimize the reductive borylmetallation/silylation (Table 2). A solution of **1a** with an alkoxyborane and a solution of $LiC_{10}H_8$ were mixed with extreme efficiency to make a homogeneous solution in **M1**. The mixture flows from **M1** to **M2** through **R1**, where the rapid formation of the radical anion (step 1), reaction with alkoxyborane (step 2) and subsequent single-electron reduction (step 3) occurred in succession to give intermediate **I**. Finally, silylation with Me_3SiOTf in **M2** and **R2** yielded the desired borylsilylated product **2aa**. When $B(OMe)_3$ and $B(O^iPr)_3$ were used as the alkoxyborane, the yields of **2aa** were low (entries 1 and 2). The use of pinacol-protected alkoxyboranes (entries 3–5) significantly improved the yield of **2aa**, with EtOBpin giving the best result (entry 4). The effect of temperature was investigated (entries 6–8), and the product **2aa** was obtained in 84% yield at −20 °C (entry 6). A large amount of **4** was obtained at −78 °C, which suggests that the reduction of alkyne (step 1) did not sufficiently proceed due to the low temperature (entry 8). A longer residence time led to lower yields of **2aa** (entries 6 and 9–11), probably due to the instability of intermediate **I** (see below). To evaluate the mixing effect, the residence time was set at 0.14 s and the total flow rate at **M1** was changed (entries 6, 12 and 13). At slower flow rates, the reaction efficiency and selectivity were drastically decreased, and a large amount of **1a** was recovered. Furthermore, mixer **M1** with a larger internal diameter resulted in lower yields and selectivity (Supplementary Table 5). Therefore, the mixing between the substrate and reductant is crucial to improve the yield and selectivity.

Scope of borofunctionalization

Under optimized conditions (Table 2, entry 6), reductive borylmetallation in flow microreactors generated intermediate **I** with high efficiency, and subsequent reactions with a variety of second electrophiles generally proceeded with exclusive *syn* selectivity (Table 3).

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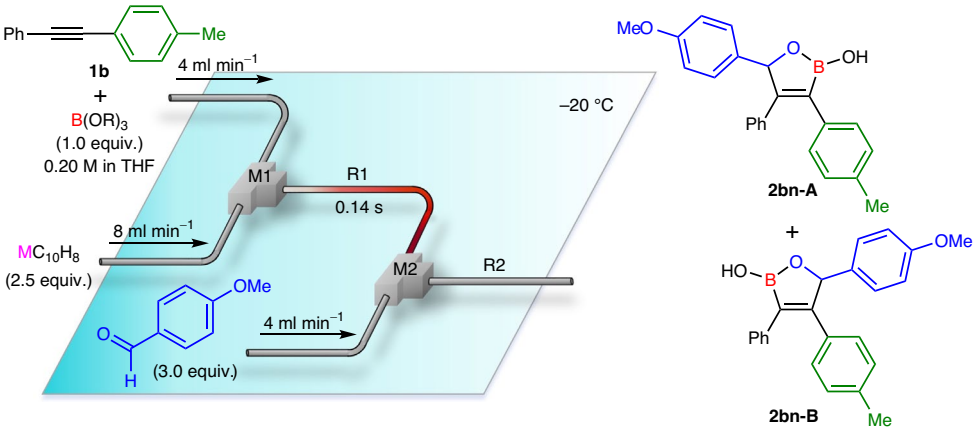
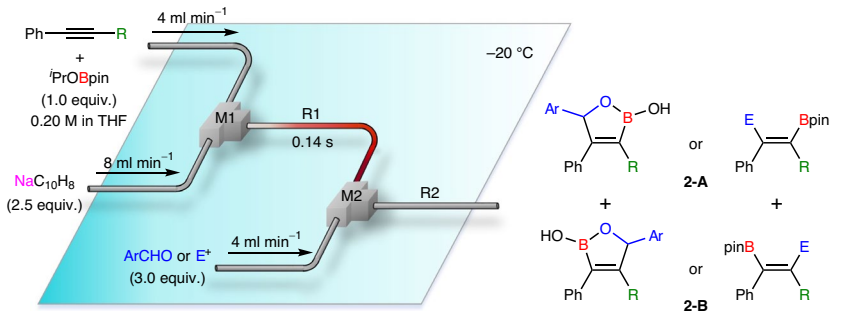
Table 4 | Regioselectivity of reductive borofunctionalization of phenyl *p*-tolyl acetylene

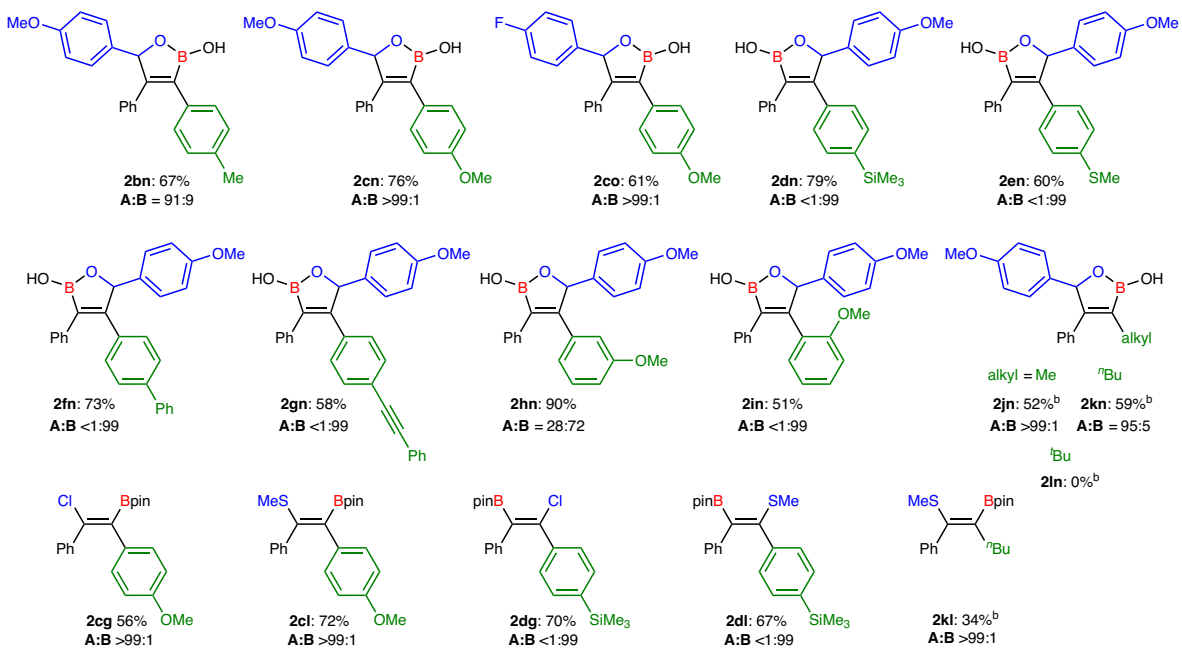


Entry	$B(OR)_3$	$MC_{10}H_8$	NMR spectroscopic yield (%)[a]		Ratio of A/B
			2bn-A	2bn-B	
1	EtOBpin	$LiC_{10}H_8$	44	26	63/37
2	EtOBpin	$NaC_{10}H_8$	52	9	85/15
3	MeOBpin	$NaC_{10}H_8$	45	9	83/17
4	^{i}PrOBpin	$NaC_{10}H_8$	60	6	92/8

[a]Yields were determined by ^{1}H NMR spectroscopic analysis using mesitylene as an internal standard.

Table 5 | Regioselectivity in borofunctionalization of unsymmetric alkynes[a]





[a]The major regioisomer of each product is shown. [b]LiDTBB was used instead of $NaC_{10}H_8$.

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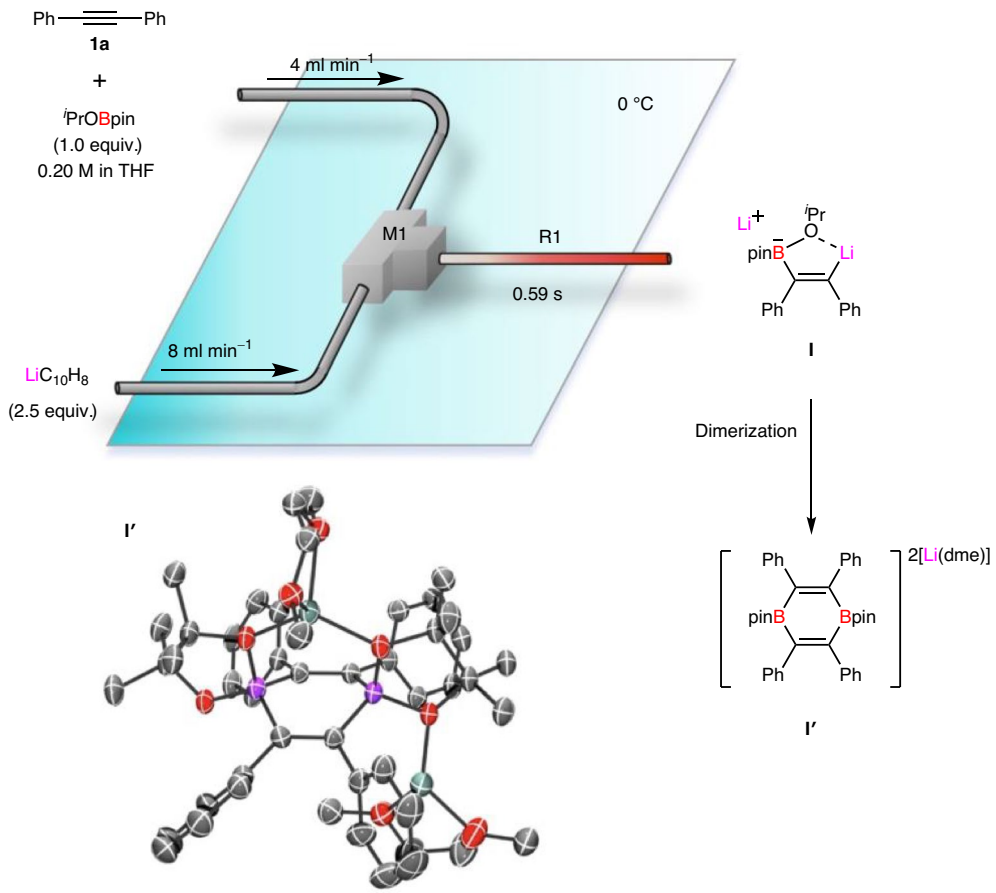

Fig. 2 | Attempt to isolate intermediate I. The attempt to isolate **I** was unsuccessful, and a six-membered dimer was obtained instead, which indicates that **I** is unstable and easily dimerizes. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms are omitted for clarity. dme, 1,2-dimethoxyethane.

An exception is the stannylation, yielding **2ad**, still in an excellent *E*:*Z* ratio of 96:4. Alkenyllithium **I** exhibited excellent reactivity, facilitating carbon–carbon bond formations with methyl triflate, benzonitrile and phenylisocyanate, which resulted in good yields of **2ae**, **2ai** and **2aj**, respectively. Additionally, a nucleophilic aromatic substitution reaction of hexafluorobenzene using $NaC_{10}H_8$ proceeded to give **2ao** by exploiting the higher nucleophilicity of the alkenylsodium intermediate. Electrophilic halogenation of **I** with NFSI, hexachloroethane and tetrabromomethane yielded **2af**–**2ah**. Furthermore, borylphosphonylation and borylchalcogenations led to high yields of **2ak**–**2an**. A nucleophilic aromatic substitution reaction of hexafluorobenzene gave borylarylation product **2ao**. The *syn* selectivity of the borofunctionalization was determined by X-ray diffraction analysis of products **2af**, **2ag**, **2ah** and **2ao** and by nuclear Overhauser enhancement spectroscopy analysis of the rest of the products.

As the second electrophiles, aldehydes and ketones underwent annulation with **I** to form oxaboroles, which are of significant interest as they represent a key skeleton in materials and pharmaceutical sciences[43,44]. The reaction conditions were found to be compatible with methoxy, fluoro and ester groups, as evidenced by the formation of **2aq**–**2as**. Additionally, aromatic, aliphatic and cyclic ketones were applicable to yield the corresponding oxaboroles (**2at**–**2av**).

Regioselectivity in the reactions of unsymmetric alkynes

To investigate the regioselectivity of the borylmetallation, unsymmetric phenyl *p*-tolyl acetylene (**1b**) was used as a substrate (Table 4). Under optimized conditions, low regioselectivity was observed (entry 1); this was unsurprising due to the small difference between phenyl and *p*-tolyl. However, the use of $NaC_{10}H_8$ instead of $LiC_{10}H_8$ resulted in a significant improvement in regioselectivity (entry 2). Furthermore, the use of ^{i}PrOBpin as the borylating agent led to the best regioselectivity in favour of **2bn-A** (entry 4). It is worth noting that conventional transition-metal-catalysed borylmetallation exhibits low regioselectivity for unsymmetric diarylacetylenes having small electronic and steric differences[45–48].

Regioselectivity in the reactions of various unsymmetric diarylacetylenes was examined (Table 5). *p*-Methoxy-substituted alkyne **1c** provided the corresponding oxaboroles **2cn-A** and **2co-A** with exclusive regioselectivity. Conversely, alkynes bearing functional groups such as trimethylsilyl, methylsulfanyl, phenyl and phenylethynyl, which are not so electron-donating as the methoxy group, afforded the opposite regioisomers **B** for **2dn**–**2gn**. The regioselectivity in the reaction of phenyl *m*-methoxyphenyl acetylene (**1h**) was low in favour of regioisomer **B**, probably because a *meta*-methoxy group generally serves as a weakly electron-withdrawing group. Moreover, phenyl *o*-methoxyphenyl acetylene (**1i**) selectively yielded regioisomer **B**, presumably due to steric control in the borylation step. With the stronger reducing reagent lithium 4,4′-di-*tert*-butylbiphenylide (LiDTBB), alkyl arylacetylenes **1j** and **1k** were reduced to synthesize oxaborole **2jn-A** and **2kn-A** in 52% and 59% yields, respectively, with complete regioselectively. 1-Phenyl-3,3-dimethyl-1-butyne (**1l**) and aliphatic alkynes such as 4-octyne did not participate in the reductive process. An attempt to convert phenylacetylene that has a terminal acidic proton gave a complicated reaction mixture. The excellent regioselectivity is general; other electrophiles including hexachloroethane and dimethyl disulfide were also used for the regioselective difunctionalization of unsymmetric alkynes to yield **2cg**, **2cl**, **2dg**, **2dl** and **2kl**. It is noteworthy that the regioselectivity observed in

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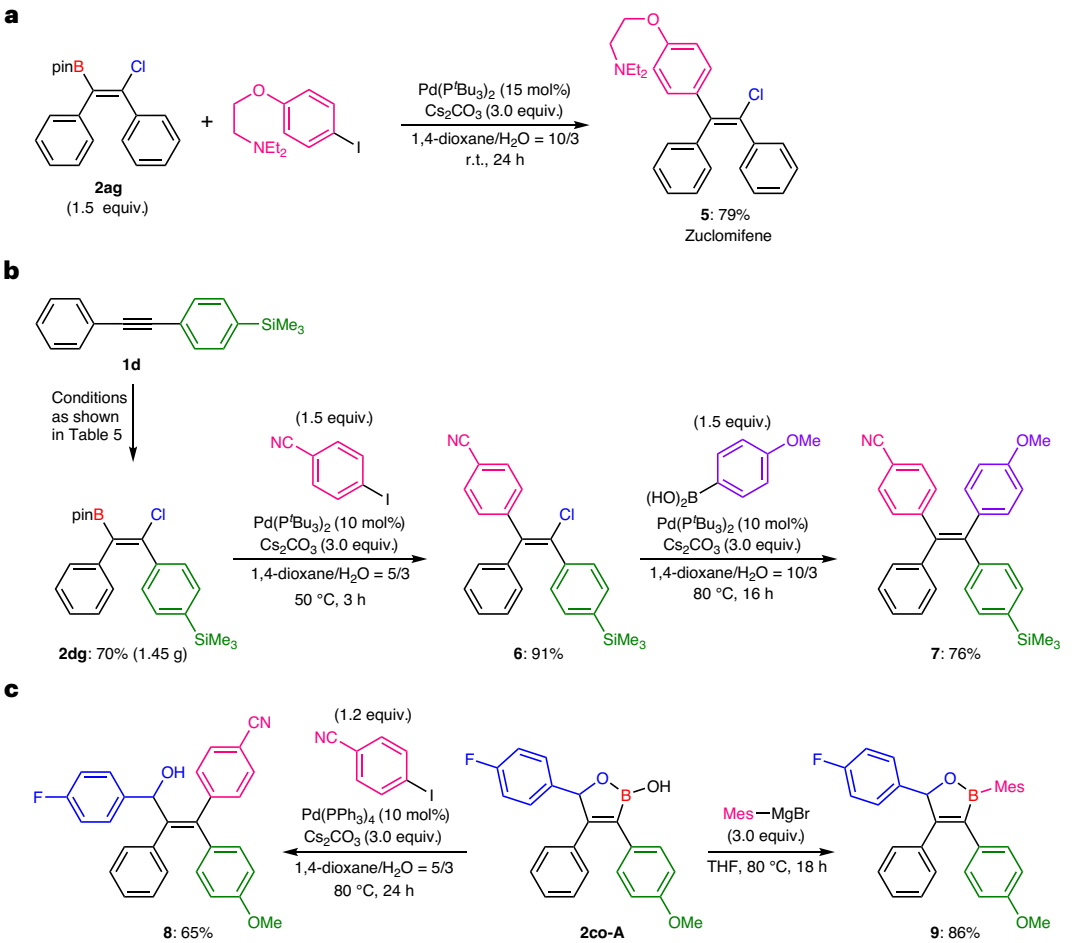

Fig. 3 | Transformations of borofunctionalization products. a, Synthesis of zuclomifene. **b**, Synthesis of stereo- and regiodefined tetraarylethene. **c**, Transformations of oxaborole. Suzuki–Miyaura coupling (left) and nucleophilic substitution of the hydroxyl group using a Grignard reagent (right). Mes, mesityl(2,4,6-trimethylphenyl).

Table 5 was determined by X-ray diffraction analysis of representative products **2cn** and **2gn** and by nuclear Overhauser enhancement spectroscopy analysis for the rest.

In general, the boron atom was installed at the vinylic carbon bearing the more electron-donating substituent. We are tempted to rationalize the high regioselectivity, specifically in the regio-determining borylation step, as follows although the exact reasons are unclear at this stage. For simplicity, we discuss alkyne **1c** and product **2cn**, which have an electron-donating methoxy group, and **1d** and **2dn**, which have an electron-withdrawing trimethylsilyl group[49,50]. We performed DFT calculations on the radical anions of **1b**, **1c** and **1d** using sodium as the countercation to obtain nucleophilicity parameters by the Fukui functions (f^-)[51] of the acetylenic carbons of the radical anions (Supplementary Figs. 10–12). Although the differences in the f^- values are too small to explain the high regioselectivity, they nevertheless imply a trend in regioselectivity. We further performed DFT calculations on the reactions of the radical anions of **1c** and **1d** with ^{i}PrOBpin. The computed reaction profiles are consistent with experimental results (Supplementary Figs. 17 and 18), that is, the pathway to the major regioisomer has a lower activation barrier than that to the minor isomer. Distortion/interaction analyses[52,53] (Supplementary Fig. 20 and Supplementary Table 11) suggest that the strain terms in the cationic component, [Na(thf)(κ^2-^{i}PrOBpin)]$^+$, in the transition states play a key role in determining the regioselectivity and that the countercation and the departing *B*-alkoxy group are hence influential as shown in Table 3.

Attempt to isolate intermediate I

To clarify the reaction mechanism, an attempt was made to isolate intermediate **I** (Fig. 2). Unfortunately, the isolation of intermediate **I** was unsuccessful because dimerization of **I** proceeded very smoothly even at −78 °C. The dimer structure was unambiguously confirmed to be **I′** by recrystallization from 1,2-dimethoxyethane (Supplementary Information). The lower yields with longer residence times in entries 9–11 of Table 1 could be attributed to the formation of less reactive dimers of **I**. It is worth noting that treatment of dimer **I′** with MeI or Me_3SiCl did not afford the corresponding difunctionalized product **2aa** or **2ae**.

Transformations of the reaction products

The Suzuki–Miyaura cross-coupling of borylchlorinated product **2ag** directly yielded zuclomifene (**5**), which is the *Z* isomer of the drug molecule clomifene, which is sold as a mixture of stereoisomers and usually requires multistep synthesis[54] (Fig. 3a). Flow synthesis is easily scalable, and the gramme-scale borylchlorination of **1d** yielded **2dg** in 70% yield (Fig. 3b) with a productivity calculated to be 50 mmol h^{-1}. Subsequent cross-coupling reactions of **2dg** with 4-iodobenzonitrile and then with 4-methoxyphenylboronic acid provided tetraarylethene **7** bearing four different aryl groups and having exclusive regio- and stereoselectivity. Although tetraarylethenes have gained significant attention for their characteristic properties such as aggregation-induced emission[5,6,55], installation of four different aryl groups on one ethene unit remains challenging and often requires lengthy steps[8–10].

Finally, transformations of oxaborole **2co-A** were also performed (Fig. 3c). The Suzuki–Miyaura cross-coupling provided tetrasubstituted alkene **8** bearing four different substituents. The hydroxy group of **2co-A** was easily transformed into a mesityl group using a Grignard reagent to give *B*-aryloxaborole **9**.

Conclusion

The utilization of flow microreactors has enabled reductive *syn*-borylithiation and *syn*-borylsodiation of arylacetylenes using alkali metal arenides and reduction-resistant trialkoxyborane. Fast mixing of a solution of alkyne and an equimolar amount of alkoxypinacolborane with a solution of metal arenide is crucial for the borylmetallation. The intermediates can be generated in the absence of electrophiles, which has enabled various borofunctionalizations to yield a variety of multisubstituted alkenes including oxaboroles. Moreover, unsymmetric alkynes undergo highly regioselective *syn*-borylmetallation, which is difficult to achieve using conventional methods involving a transition metal catalyst. The products are versatile intermediates, some of which have been transformed into a drug molecule and tetraarylethene bearing four different aryl groups. We have demonstrated the potential of reductive borylmetallation in organic synthesis. Further investigation into the origin of the exclusive regioselectivity and the utility of unsymmetric dimetallation is ongoing in our laboratory.

Methods

General procedure for reductive borofunctionalization of alkyne using flow microreactors

A flow microreactor system consisting of an anchor-shaped micromixer (M1), a T-shaped micromixer (M2), two microtube reactors (R1, R2) and three precooling units (P1, P2 and P3: inner diameter, 1,000 μm; length, 100 cm) was used. The flow microreactor system was immersed in a cooling bath (−20 °C). A solution of arylacetylene **1** containing EtOBpin (0.20 M in THF; flow rate, 4 ml min^{-1}), and a solution of $LiC_{10}H_8$ (0.25 M in THF; flow rate, 8 ml min^{-1}) were introduced into M1 (inner diameter, 250 μm) using syringe pumps, and the mixed solution was passed through R1 (length, 3.5 cm; inner diameter, 1,000 μm). A solution of electrophile (0.60 M in THF; flow rate, 4 ml min^{-1}) was introduced into M2 (inner diameter, 500 μm) using a syringe pump, and the resulting solution was passed through R2 (length, 200 cm; inner diameter, 1,000 μm). After a steady state was reached, the product solution was collected into a vial with saturated aqueous NH_4Cl for 15 s (0.2 mmol scale). The resulting biphasic solution was extracted three times with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification gave product **2**.

Data availability

Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2247528 (**2af**), CCDC 2224345 (**2ag**), CCDC 2224346 (**2ah**), CCDC 2247529 (**2an**), CCDC 2224347 (**2ao**), CCDC 2224348 (**2cn**), CCDC 2224349 (**2gn**) and CCDC 2224350 (**I′**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. The data supporting the findings of this study, including NMR spectra, mass spectra and melting points of synthesized compounds and Cartesian coordinates for the computational study, are available in the Supplementary Information.

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Author contributions

Y.J. and H.Y. conceived and designed the project. Y.J. and T.K. performed the experiments. T.K. performed the X-ray crystallography and computational chemistry. All authors contributed to the writing and editing of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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