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Article

Synthesis of *anti*-vicinal diboronates from diarylethynes and B_2pin_2

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ABSTRACT

Anti-vicinal diboronates were fabricated from easily available diarylethynes and B_2pin_2 via a base-catalyzed domino-borylation-protodeboronation (DBP) strategy under transition-metal-free conditions. Under the standard conditions, reactants with a range of different classes of functional groups on the rings, such as MeO, MeS, CF_3O, Me_2N, TMS, I, Br, Cl, F, and the thiophene ring, were tolerated. Downstream transformation of the vicinal diboronates provided a facile pathway for obtaining vicinal diols by mild oxidation with $NaBO_3$, and a new deuteration technique was developed in order to acquire 1,2-diarylethanes-1,2-d_2 and 1,2-diarylethanes-1,1,2,2-d_4. The new deuteration strategy developed in this study may provide a new research direction for deuteration chemistry.

1. Introduction

Boronic acids and their esters are an integral part of materials science, chemical sensors, bioactive molecules, and drug molecules [1–4]. Organic compounds containing boryl units are paramount intermediates in synthetic chemistry because the C–B bond can be converted into a rich set of functional groups [5–7]. Multi-borylated compounds are particularly attractive because they can be selectively converted into multiple C–X bonds to build versatile complex molecules [6]. The borylation of unsaturated substrates, such as the base-promoted boronation of alkynes, is one of the most effective ways to synthesize polyboronates [8–13]. Nevertheless, the synthesis of vicinal alkyl diboronates from alkynes is underexplored, whereas the synthesis of vicinal diboronates from alkenes is well known [14–17].

To date, only four studies on such reactions have been published. In 2009, Hoveyda's group [18] developed a method for the enantio-selective construction of vicinal diboronates from terminal alkynes and B_2pin_2 using NHC-Cu-catalysis (Scheme 1a). In 2012, Yun's group [19] reported the copper-catalyzed diborylation of silylacetylenes to produce *syn*-vicinal diboronates (Scheme 1b). In 2017, our group [9] developed a base-controlled highly selective protocol for the synthesis of vicinal diboronates from terminal alkyl alkynes via domino-borylation-protodeboronation (DBP) with stoichiometric base (Scheme 1c). In 2019, Yorimitsu's group [20] developed a technique for the diborative reduction of alkynes to 1,2-bisboronates (a mixture of threo- and erythro-configuration) with the alkali metal sodium in two steps (Scheme 1d). Vicinal diboronates are potentially effective intermediates for the construction of polyarylethanes and vicinal diols. Polyarylethanes are valuable frameworks in medicinal and materials chemistry [21,22]. Therefore, the development of a simple method to achieve vicinal diboronates **2** is urgent and necessary. Despite the great advances in the 1,2-diboronation of alkynes, the highly selective synthesis of alkyl 1,2-bisboronates from diarylethynes has not yet been reported (Scheme 1e). There are several challenges in this transformation: (1) two benzylic C–B bonds are formed; these bonds are labile and generally susceptible to protodeboronation under basic conditions, leading to saturated diarylethanes; (2) the non-terminal acetylene species hinder diborylation of the substrates under known conditions; (3) it is difficult to achieve high diastereoselectivity.

2. Materials and methods

2.1. General methods

All reagents and solvents were purchased from Adamas Reagent, Energy Chemical Company, Bide Pharmatech Ltd., and Tansoole, and were used without further purification. Unless otherwise stated, all reactions were accomplished in Schlenk tubes under N_2 atmosphere. The reactions were monitored by thin layer chromatography (TLC) or gas chromatography-mass spectrometry (GC–MS). Flash column chromatography was performed over silica gel (200–300 mesh). ^1H NMR spectra were recorded on a Bruker

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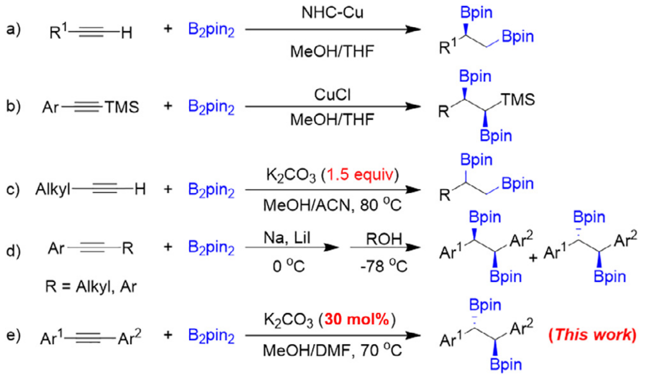


Scheme 1. (Color online) Synthesis of vicinal diboronates from alkynes.

Avance III 500 MHz NMR spectrometer, and the chemical shifts (in ppm) were referred to $CDCl_3$ (δ = 7.26 ppm) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometer and were calibrated with $CDCl_3$ (δ = 77.0 ppm). ^{11}B NMR spectra were acquired with accessories on the same NMR spectrometer using $CDCl_3$. High-resolution mass spectra (HRMS; (ESI)) were acquired with quadrupole and time-of-flight (TOF) mass spectrometers.

2.2. General procedure for synthesis of anti-vicinal diboronates

B_2pin_2 (3.5 equiv, 0.7 mmol), diphenylethyne (0.2 mmol), and K_2CO_3 (0.3 equiv, 0.06 mmol) were added to a 25 mL Schlenk tube. MeOH (10 equiv) and DMF (0.2 mL) were then added under nitrogen atmosphere. The Schlenk tube was sealed and stirred at 70 °C for 24 h. Thereafter, the reaction mixture was extracted with NH_4Cl (aq.)/ethyl acetate (EA) and the organic layers were dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by silica gel chromatography to afford the product.

3. Results and discussion

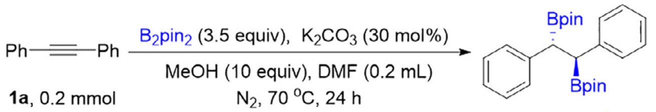
3.1. Optimization of reaction conditions

We commenced our study by using diphenylethyne (**1a**) and B_2pin_2 as the model substrates for optimization of the reaction (Table 1). This transformation proceeded smoothly under the standard conditions and gave the vicinal diboronates (**2a**) with an isolated yield of 84% (Table 1, entry 1). When the amount of B_2pin_2 was decreased from 3.5 equiv to 2.0 equiv, the yield declined steeply from 90% to 63% (Table 1, entries 1–4). When the transformation was performed at higher temperature (80 °C), the yield decreased significantly because of protodeboronation (Table 1, entries 4, 5). The effects of solvents on this transformation were investigated (Table 1, entries 6, 7). The common ether solvents (THF, Et_2O) were unfavorable for the reaction. The presence of air also had a detrimental effect on the reaction (Table 1, entry 8).

3.2. Extension of substrate scope

Having determined the optimal reaction conditions, a series of diarylalkynes was investigated for this base-catalyzed vicinal diborylation reaction (Table 2). Diarylalkynes containing a wide range of functional groups were successfully tolerated in the reaction, giving the *anti*-1,2-diboronates in good yields (**2a**–**w**). The relative stereochemistry of compound **2d** was unambiguously confirmed by X-ray analysis. A series of new diboronate compounds containing two successive chiral centers was observed. Substrates **1b**–**j**,

Table 1
Optimization of conditions for double hydroborylation of 1,2-diphenylethyne (1a).



1a, 0.2 mmol

2a, 84% [a]

Entry	Variation from the standard conditions	Yield (%)[b]
1	KO^{t}Bu or K_2CO_3	90(84[a])
2	B_2pin_2 (3.0 equiv), KO^{t}Bu	80
3	B_2pin_2 (2.5 equiv), KO^{t}Bu	72
4	B_2pin_2 (2.0 equiv), KO^{t}Bu	63
5	B_2pin_2 (2.0 equiv), KO^{t}Bu, 80 °C	50
6	B_2pin_2 (2.0 equiv), THF (0.2 mL)	17
7	B_2pin_2 (2.0 equiv), Et_2O (0.2 mL)	Trace
8	KO^{t}Bu	70[c]

[a] Isolated yield.
[b] GC yield.
[c] Under air.

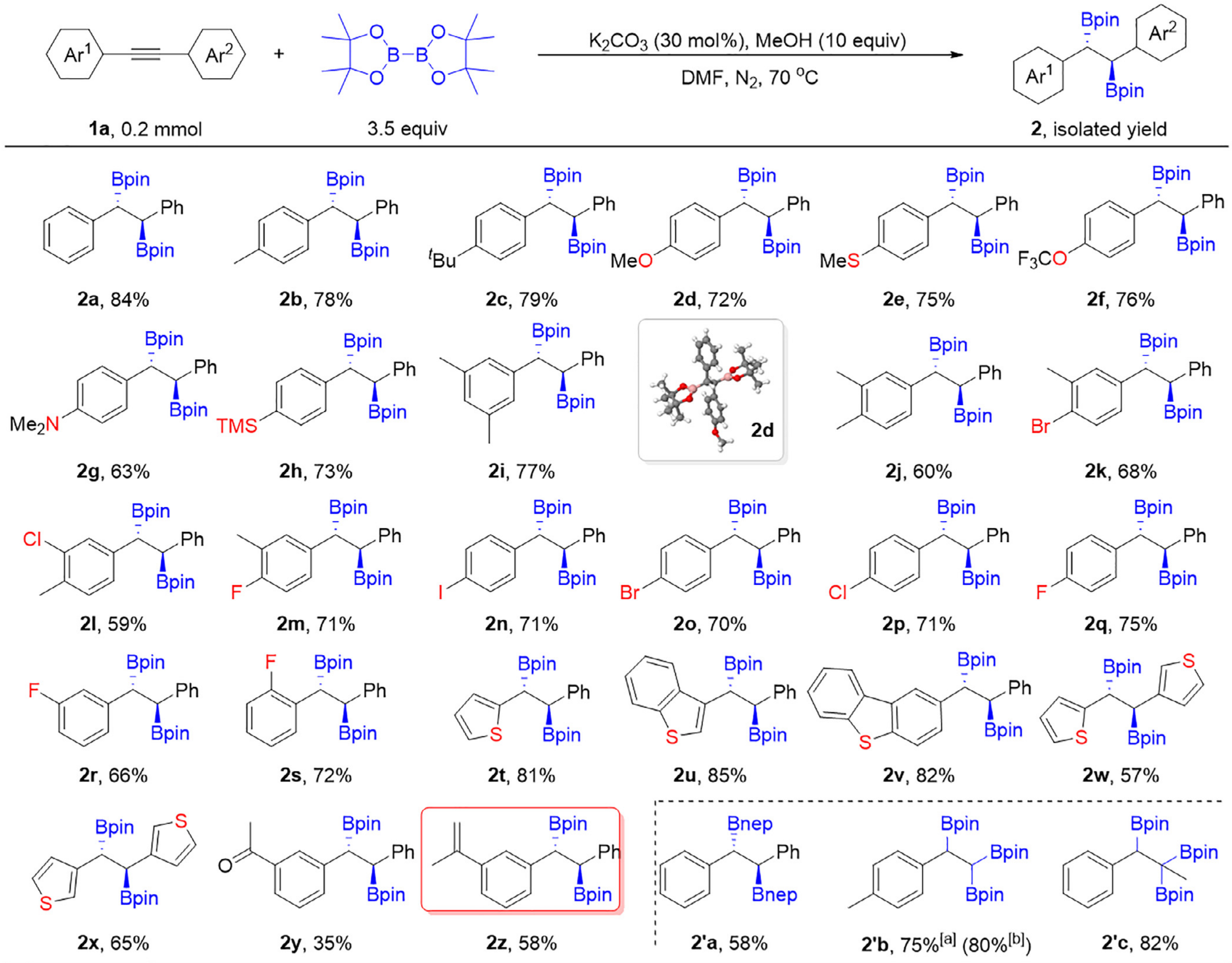
with different electron-donating groups (such as Me, ^{t}Bu, MeO, MeS, CF_3O, Me_2N, TMS) on the rings, could afford the corresponding products in good yields. Substrates bearing a halogen substituent (I, Br, Cl, F) were also examined under the standard conditions and the results were satisfactory (**2k**–**s**). Alkynes with disubstituted benzene rings were also suitable substrates for the reaction (**2i**–**m**). Notably, labile substituents such as TMS, Br, and I were well tolerated under the standard conditions (**2h**, **2k**, **2n**, **2o**). Substituents on different positions (*ortho* or *meta* or *para*) of the aromatic ring did not affect the efficiency of this transformation (**2q**–**s**). Diarylalkynes containing a thiophene ring also provided the desired products in high yields (**2t**–**x**). When a strong electron-withdrawing group is present on the *para*-position of the benzene ring, the boron in the benzyl group is unstable and is easily protonated [8,10,20]. This issue was encountered herein, and after many attempts (see Supplementary materials (online) for unsuccessful substrates), it was surprisingly found that **2y** could be obtained in medium yield (35%) under the present conditions, though the Ac group on the *meta*-position of the benzene ring. Notably, the C=C double bond was well tolerated under the standard conditions (**1z**). When B_2pin_2 was changed to B_2nep_2, the transformation progressed smoothly (**2′a**). When ethynylbenzene, trimethyl(phenylethynyl)silane, and prop-1-yn-1-ylbenzene were subjected to the standard conditions, the corresponding 1,1,2-triboronates were obtained (**2′b**, **2′c**). Although the desired products were not obtained, this observation suggests that the reaction mechanism could involve DBP [9].

3.3. Application of 1,2-diborate-1,2-diarylethanes

To demonstrate the practical utility of the transformation, a gram-scale reaction was performed, and the product **2a** was obtained in 75% yield without significant loss of efficiency (Scheme 2a). *Anti*-1,2-diboronate (**2a**) was oxidized with $NaBO_3$ to lead to the *anti*-vicinal diol (**3a**) in 81% yield (Scheme 2b), which provided a facile strategy for obtaining such diols via readily available starting materials. Notably, vicinal diols are essential structural subunits that are frequently found in biologically active natural products [23]. *Anti*-1,2-diboronate (**2a**) was also easily converted to the more stable borate **4a** (Scheme 2c).

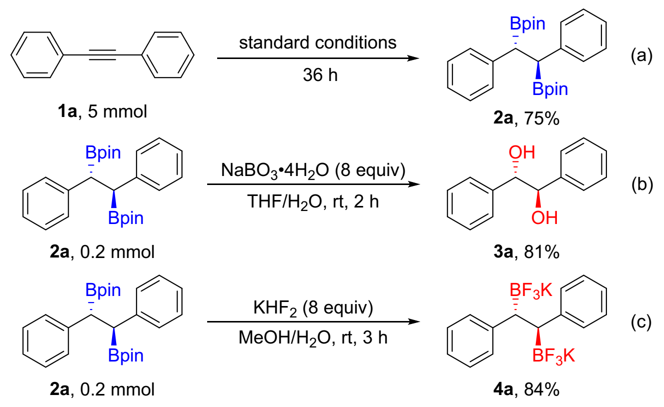
The above strategy represents a fast, efficient, and high yield protocol with high deuterium-incorporation for the selective deuteration of diarylalkynes (Table 3). Firstly, CH_3OH was used as a proton source with diarylethynes **1** to synthesize

Table 2
Synthesis of vicinal diboronates from diarylethynes.



[a] From 1-ethynyl-4-methylbenzene.
[b] From trimethyl(p-tolylethynyl)silane.

1,2-diborate-1,2-diarylethanes **2**, which were then subjected to CD_3OD and Cs_2CO_3 at 70 °C to afford 1,2-diarylethanes-1,2-d_2 (**5a–l**) in excellent yields with excellent deuterium incorporation ratios. Notably, the reaction of **1** with CD_3OD initially produced the corresponding 1,2-diborate-1,2-diarylethanes-1,2-d_2 **6**, which were subsequently converted to 1,2-diarylethanes-1,1,2,2-d_4 (**7a–k**) using the same conditions described for the synthesis of **5**. The development of deuterium protodeboronation will certainly be an important supplement to the known deuteriation reactions. The structure of **6a** was confirmed by X-ray crystallographic analysis, showing high *anti*-selectivity.

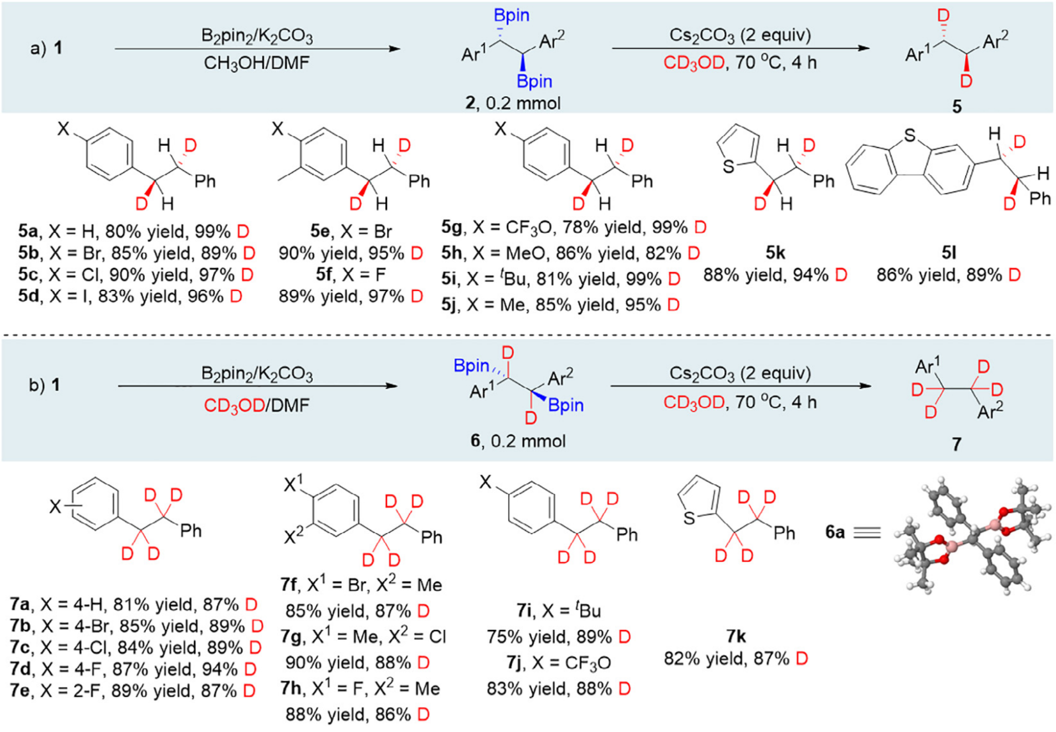


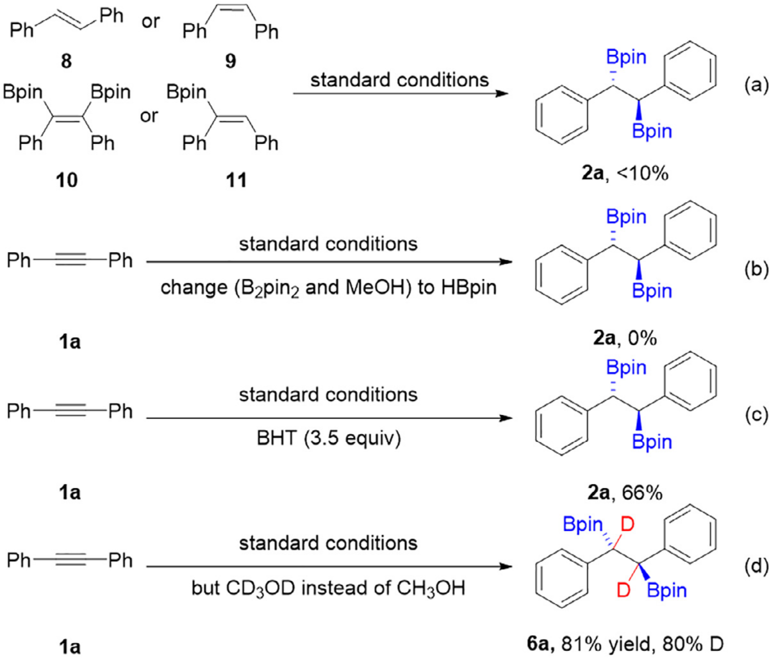
Scheme 2. (Color online) Scale up and application of 1,2-diborate-1,2-diarylethanes.

3.4. Study of reaction mechanism

To understand the reaction mechanisms, compounds **8**–**11** were subjected to the standard diborylation conditions; however, the desired product **2a** was not obtained (<10% yield, Scheme 3a). Therefore, it is unlikely that these compounds are intermediates in this reaction. When we replaced B_2pin_2 and MeOH with HBpin in the diborylation reaction, no product (**2a**) was obtained (Scheme 3b). We also ruled out the possibility of a free radical mechanism due to the negative result of the radical trapping experiment (Scheme 3c). The reaction was also performed with MeOH d_4 instead of MeOH under the standard conditions, and

Table 3
Deuteration of diaryl acetylenes to selectively yield deuterated diarylethanes.

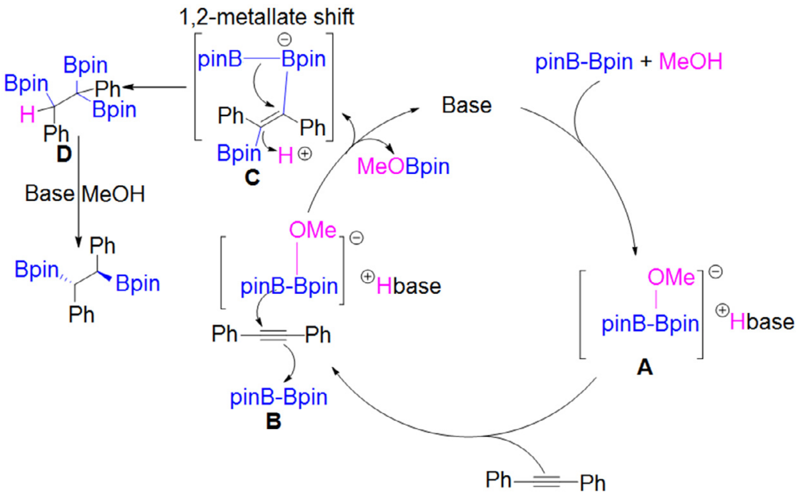




Scheme 3. (Color online) Control experiments.

the highly *di*-D vicinal diboronates **6a** were obtained in 81% yield with 80% deuterium incorporation (Scheme 3d), which suggests that methanol is the proton source in the reaction.

Based on the previous reports [8–14,24–30] and the above experiments, we proposed a mechanism for the construction of *anti*-vicinal diboronates, as depicted in Scheme 4. Firstly, B_2pin_2 in the presence of MeOH and a catalytic base generates the activated and nucleophilic species **A** ($[BaseH]^+.[B_2pin_2.MeO]^-$) [14,16,30] *in situ*, which further attacks the C—C triple bond of diphenylethyne, while the activated alkyne attacks another B_2pin_2, leading to the adduct **B**. Along with the formal departure of MeOBpin from the adduct **B**, the base is recovered, and adduct species **C** is formed, which undergoes a 1,2-metallate shift to deliver 1,1,2-tris(boronate) **D**. Under the basic conditions with



Scheme 4. (Color online) Proposed mechanism.

methanol, the *geminal* Bpin moieties preferentially undergo protodeboronation to yield the final products 1,2-bis(boronates). It is thought that due to steric hindrance, vicinal diboronates with *anti*-selectivity are formed.

4. Conclusions

In summary, we developed an expedient strategy for the diastereoselective synthesis of *anti*-vicinal diboronates with two adjacent stereocenters under transition-metal-free conditions. The standard conditions were compatible with a range of functional groups on the rings, such as MeO, MeS, CF_3O, Me_2N, TMS, I, Br, Cl, F, vinyl, and thiophene. The diastereoselective *anti*-vicinal diboronates were effectively oxidized with $NaBO_3$ to render vicinal diols. Further, the products were easily converted into more stable borates with KHF_2, and easily deuterated with CD_3OD in the presence of Cs_2CO_3, to afford 1,2-diarylethanes-1,2-d_2 or 1,2-diarylethanes-1,1,2,2-d_4. It is anticipated that the deuteriation strategy developed in this study will inspire developments in deuteriation chemistry, and complement our previously reported DBP strategy. The proposed mechanism suggests that this is a synergistic process between two molecules of B_2pin_2 and diarylethynes.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Author contributions

Zhijie Kuang performed the experiments and provided the manuscript. Shaoyu Mai provided assists for the single-crystal testing and analysis. Kai Yang gave suggestions on mechanism study. Qiuling Song raised the idea of diborylations, guided Zhijie Kuang performing experiments and revised the manuscript.

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2019.09.015.

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