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trans-Hydroboration of Propiolamides: Access to Primary and Secondary (*E*)-β-Borylacrylamides

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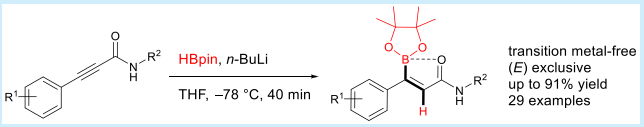
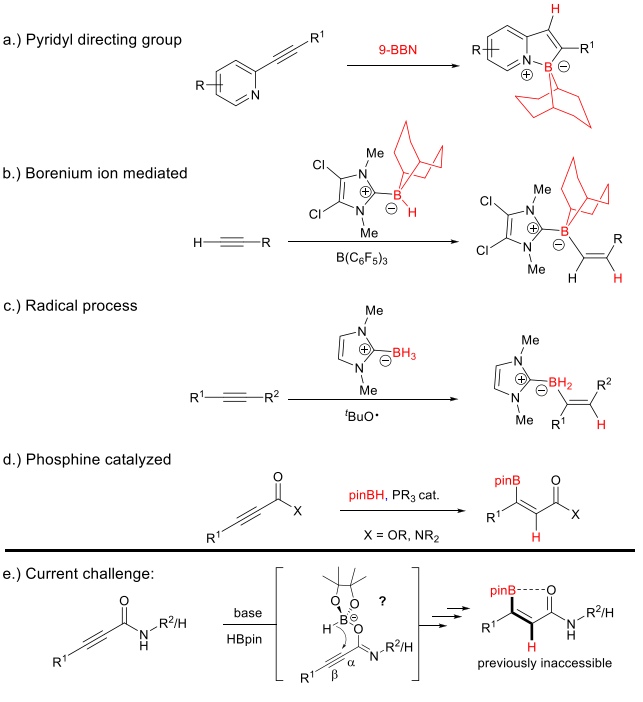
Supporting Information

ABSTRACT: A base-mediated *trans*-hydroboration of propiolamides that provides access to previously elusive primary and secondary (*E*)-β-borylacrylamide products has been developed. In the presence of *n*-butyllithium and pinacolborane, complete regioselectivity and stereoselectivity is observed, affording the corresponding vinylboronate products in up to 91% yield. A wide variety of primary and secondary amides served as efficient substrates for this transformation. A plausible reaction mechanism that involves substrate-assisted activation and a key intramolecular cyclization is discussed.



The boronic acid moiety has emerged as one of the most versatile functional groups in modern organic synthesis, because of its versatility in many chemical transformations. Most notable is their use as substrates in Suzuki−Miyaura cross-coupling reactions.[1] Notwithstanding their importance in complex molecule synthesis, boron-containing compounds are also valuable in medicinal chemistry, as five small molecule organoboron drugs have been approved by the FDA.[2] Thus, methods for their synthesis are needed. Classical hydroboration of C≡C bonds using trivalent borane reagents generate organoboron compounds with *cis* configuration;[3] the resulting alkenylboronates are particularly advantageous, because of their desirable stability and reactivity profiles.[4] More recently, reports of hydroboration of terminal alkynes provide access to previously elusive (*Z*)-vinylboronates.[5] The more challenging transformation includes the corresponding hydroboration reactions of internal alkynes affording the *trans*-addition products (see Scheme 1). Toward this end, a handful of transition-metal-catalyzed protocols using Ru,[6] Pd,[7] and Au[8] have been developed. However, the corresponding transition metal-free *trans*-hydroboration reactions are scarce. In seminal work, Wang and Yamaguchi developed an elegant transition metal-free protocol utilizing a 2-pyridyl group as an intramolecular directing group (Scheme 1a).[9] Complete regioselectivity and stereoselectivity was observed, but the substrate scope was limited to dialkylboranes such as 9-BBN and instability of the products lead to decreased yield during isolation. An alternative approach by Ingleson and co-workers involved an *N*-heterocyclic carbene (NHC)/9-BBN complex that transfers a hydride to $B(C_6F_5)_3$ forming a borenium ion that coordinates to the alkyne facilitating the hydride transfer to afford the desired product (Scheme 1b).[10] Subsequently, Taniguchi et al. reported a radical-mediated reaction of internal alkynes with NHC-activated borane, which is catalyzed by di-*tert*-butyl peroxide (Scheme 1c).[11] Excellent regioselectivity and stereoselectivity was observed across a broad range of substrates, although terminal alkynes and alkynoates suffered from reduced yields. More recently, a phosphine-catalyzed method was independently reported by our group, as well as groups led by Sawamura and Vilotijevic (Scheme 1d).[12] The hydroboration reaction proceeded under mild conditions with <10% catalyst loading and a wide variety of alkynoate esters and tertiary propiolamides served as effective substrates affording hydroborated product in good to excellent yields. Drawbacks from these methods include limited scope with

Scheme 1. Strategies for the Transition Metal-Free *trans*-Hydroboration of Internal Alkynes



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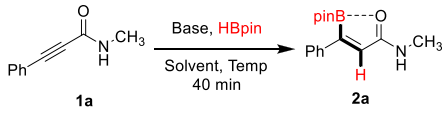
electron-deficient arenes and incomplete stereoselectivity with alkyl substrates.[12] Most notably, primary and secondary propiolamides are inert under these reaction conditions. However, the hydroboration of unsaturated amides is not unprecedented. For example, Li and co-workers recently reported the rhodium-catalyzed reversed hydroboration of substituted acrylamides, which were subsequently oxidized before isolation. The transformation proceeded efficiently with excellent regioselectivity and stereoselectivity.[13] Intramolecular coordination of the amide to rhodium in the reduced organorhodium species provided the necessary conformation for stereoselective borylation; this highlights the utility of amide coordination in substrate-driven stereoselectivity.

Inspired by these previous reports, we sought to develop a method to previously inaccessible primary and secondary (*E*)-*β*-borylacrylamides. We envisioned a Brønsted base-mediated deprotonation that facilitates the formation of a tetrahedral borohydride intermediate similar to the diboration[14] and silaboration[15] protocols recently reported by our group as well as alkynylboration methodology reported by Uchiyama[16] (Scheme 1e). We hypothesize that the borohydride complex is sufficiently activated to deliver a hydride to the *α*-carbon and subsequent *β*-borylation generates the desired product with *E* configuration.[14,16]

We initiated our studies by first confirming that the phosphine-catalyzed protocol was incompatible with propiolamide substrates. Thus, treating propiolamide **1a** with tri-*n*-butyl phosphine afforded no product, and starting materials were recovered (Table 1, entry 1). Next, we employed a strong base such as *n*-butyllithium (1.4 equiv) in the presence of 12-crown-4 and HBpin at −78 °C to afford **2a** in good yield (Table 1, entry 2). The role of the crown ether is to chelate with the Li cation and generate a naked alkoxide of **1a**, thereby increasing its Lewis basicity toward HBpin. Reducing the equivalency of reagents resulted in a minor increase in yield (Table 1, entry 3), but diluting the reaction mixture further increased the product yield (Table 1, entry 4). We presume that dilute conditions allow for more-efficient solvation of ion aggregates.[17] Excitingly, a similar yield was obtained in the absence of crown ether (Table 1, entry 5).[18] This is advantageous as crown ether coelutes with the product and is difficult to remove. Reducing the equivalency of base and pinacolborane to 1.0 had minimal impact on product yield (Table 1, entry 6). Alternative bases such as phenyllithium also efficiently mediated the transformation, albeit in slightly lower yield (Table 1, entry 7). The use of a Grignard reagent such as EtMgBr resulted in an unsatisfactory yield (Table 1, entry 8). Unfortunately, metal hydrides such as LiH do not mediate the hydroboration reaction, although the reason for this is unclear (Table 1, entry 9). We found that LiTMP and LDA also afforded **2a**, but at the cost off a modest reduction in yield (Table 1, entries 10 and 11). Weaker bases such as *t*-BuOLi or TEA were ineffective (Table 1, entries 12 and 13). We next determined the effect of solvents. Replacing THF with toluene or CPME resulted in poor yields that are likely due to reduced solubility of ionic intermediates (Table 1, entries 14 and 15). Dichloromethane as a solvent afforded **2a** in only a modest yield (Table 1, entry 16). We thus chose *n*-butyllithium as the base with THF as solvent as the optimized reaction condition (Table 1, entry 5). Characterization of **2a** by ^{11}B NMR spectroscopy suggested internal coordination between B and carbonyl oxygen (13 ppm). Following X-ray crystallographic studies, we unambiguously confirmed the *E* configuration of the alkene and internal coordination, as suggested by the B−O bond length of 1.61 Å (Figure 1, see CCDC Accession No. 1907779).

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	base/catalyst (equiv)	temperature (°C)	yield[e] (%)
1[b]	THF	*n*-Bu_3P (0.5)	60	0
2[c]	THF	*n*-BuLi (1.4)	−78	71
3[c]	THF	*n*-BuLi (1.1)	−78	73
4[d]	THF	*n*-BuLi (1.1)	−78	94
5	THF	*n*-BuLi (1.1)	−78	90
6	THF	*n*-BuLi (1.0)	−78	85
7	THF	PhLi (1.1)	−78	78
8	THF	EtMgBr (1.1)	−78	34
9	THF	LiH (1.1)	0	0
10	THF	LiTMP (1.1)	−78	68
11	THF	LDA (1.1)	−78	52
12	THF	*t*-BuOLi (1.1)	0	0
13	THF	TEA (1.1)	0	0
14	toluene	*n*-BuLi (1.1)	−78	25
15	CPME	*n*-BuLi (1.1)	−78	30
16	DCM	*n*-BuLi (1.1)	−78	64

[a]General procedure: propiolamide (0.2 mmol) was diluted in solvent (0.1 M); base (0.22 mmol) was added at −78 °C; pinacolborane (0.22 mmol) was added dropwise then the reaction was warmed to room temperature (rt). [b]1.1 equiv of pinacolborane was used and the reaction was run for 4 h at 0.6 M. [c]Reaction performed at 0.2 M with 12-crown-4 (same equiv as *n*-BuLi). [d]Reaction performed at 0.1 M with 12-crown-4 (1.1 equiv). [e]Isolated yield. CPME = cyclopentylmethyl ether; DCM = dichloromethane.

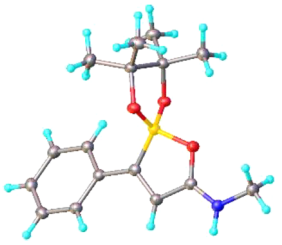


Figure 1. X-ray crystal structure of compound **2a** (CCDC Accession No. 1907779; see the Supporting Information).

With the optimal reaction conditions in hand, we sought to determine the substrate scope and limitations (Scheme 2). Increasing the steric constraint on nitrogen was well-tolerated. For example, *N*-propyl (**1b**), *N*-isopropyl (**1c**), and *N*-*tert*-butyl (**1d**) propiolamides efficiently afforded products **2b**−**2d** in good yields. Furthermore, an *N*-allyl substituted propiolamide (**1e**) was chemoselectively transformed to **2e** in the presence of a competing alkene. When the *N*-phenyl substituted propiolamide (**1f**) was treated with *n*-BuLi and HBpin, **2f** was obtained in good yield but with contamination of inseparable impurities. However, switching the base to PhLi allowed the reaction to proceed smoothly in good yield. Substitutions on the aryl moiety were also well-tolerated. Aryl substituents with electron-donating groups such as 4-methoxyphenyl (**1g**)- and 2-methoxyphenyl (**1h**)-substituted

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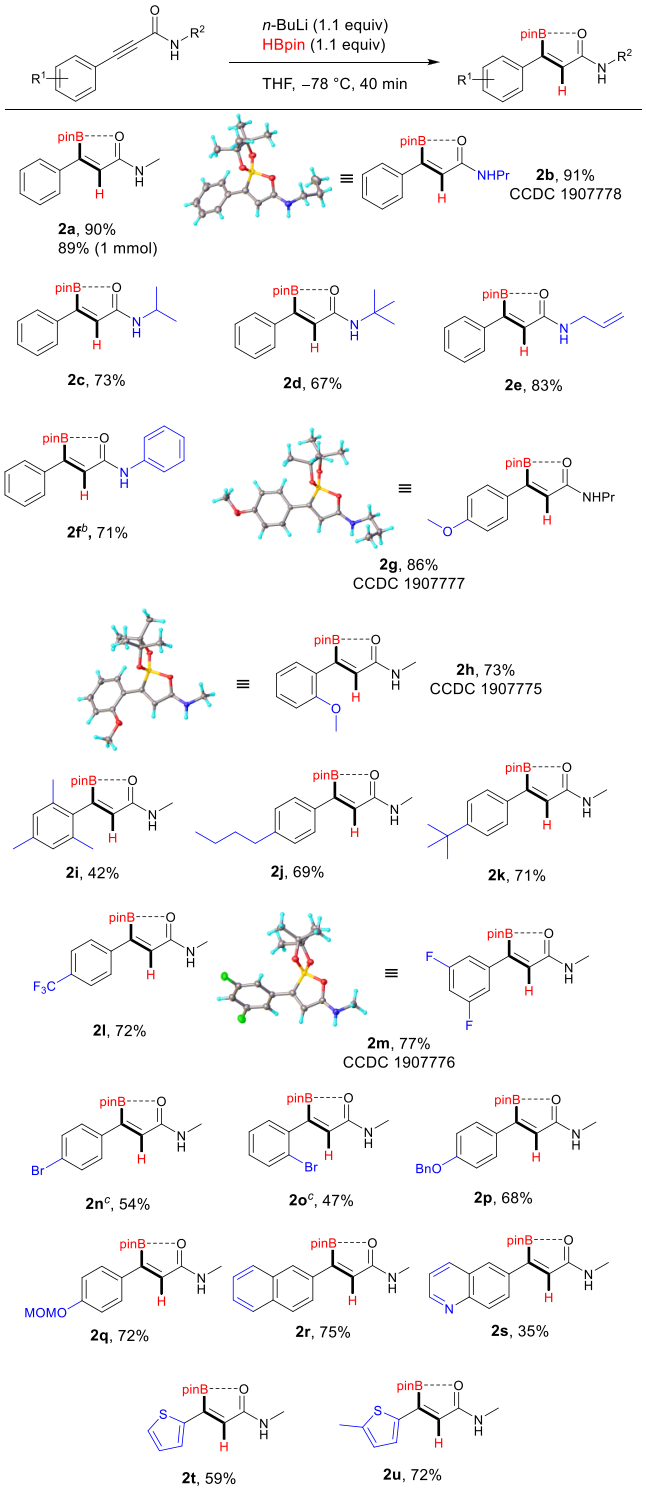
Scheme 2. Substrate Scope of Secondary Propiolamides[a]

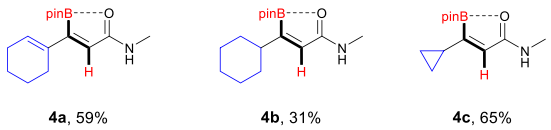


[a]General procedure: propiolamide (0.25 mmol) was diluted in THF (0.1 M) and cooled to −78 °C; *n*-butyllithium (0.275 mmol, 2.5 M in hexanes) was added at −78 °C, followed by pinacolborane (0.275 mmol); then, the reaction was warmed to rt. [b]Performed with PhLi. [c]Performed with LiTMP.

propiolamides efficiently afforded **2g** and **2h** in excellent yields. Alkyl substituents on the ring (**1i**−**1k**) were efficient substrates, although increasing the steric bulk, such as that observed in the mesityl group, was accompanied by a modest reduction in yield. Propiolamides with electron-withdrawing groups such as trifluoromethyl (**1l**) and 3,5-difluoro (**1m**) were effective substrates for this transformation and afforded products **2l**−**2m** in good yields. Bromine at the *ortho*- or *para*-position of the aryl ring provided **2n** and **2o**; however, LiTMP as a base was utilized to avoid the problematic lithium-halogen exchange with *n*-butyllithium. The reaction was also compatible with protecting groups such as benzyl and MOM, generating **2p** and **2q**, respectively. Larger rings such as naphthalene (**1r**) and heteroaryl ring systems, such as quinoline (**1s**), as well as thiophenes (**1t** and **1u**), served as good substrates generating the corresponding borylated products **2r**−**2u**. We surmised that the reduced yield for **2t** may be due to the acidic 2-H on the thiophene unit. We confirmed this by performing hydroboration on the 5-methylthiophene derivative (**1u**) and observed an increase in product yield (**2u**). Finally, we confirmed the amenability of the transformation to scale up with a 1 mmol reaction of **1a**, affording 89% isolated product (Scheme 2).

With the substrate scope of aryl substituents established, we determined the tolerance of the reaction with nonaromatic substituents (Scheme 3). In the presence of enyne **3a**, the triple bond was chemoselectively hydroborated (**4a**) in good yield. Under our reaction conditions, aliphatic substituted propiolamides **3b** and **3c** exclusively afforded single *E* isomers **4b** and **4c** in fair to good yields. However, the phosphine-catalyzed hydroboration of propiolates with cyclic alkane substituents, such as cyclohexyl and cyclopropyl, resulted in a mixture of *E* and *Z* isomers.[12a,b]

Scheme 3. Substrate Scope of Enyne and Aliphatic Secondary Propiolamides[a]



[a]General procedure: Same as in Scheme 1. After reaching rt, these reactions were heated to 66 °C for 1.5 h.

Primary amides are especially challenging for alkyne reduction since, to date, limited examples exist for this transformation.[14,15] Utilizing the developed method with 2 equiv of *n*-BuLi and pinacolborane, 3-phenylpropiolamide (**5a**) was borylated in excellent yield (Scheme 4). Other functional groups on the phenyl ring such as electron-donating methyl (**6b**) and electron-withdrawing trifluoromethyl (**6c**) were similarly generated in good yields. Whereas 5-methylthiophene (**6d**) was achieved in 61% yield, the linear alkyl-substituted **6e** was afforded in modest yield. Steric encumbrance around the *β*-carbon and the lack of resonance stabilization of the intermediate carbanion may reduce borylation efficiency (*vide infra*).

A plausible mechanistic route to explain the reactivity and stereoselectivity observed is shown in Scheme 5, similar to a previously reported mechanism for the diboration of propiolamides.[14] Deprotonation of **1a**, followed by the addition of pinacolborane, likely leads to borate complex **2I**, which, upon intramolecular hydride transfer, would yield the high-energy vinyl anion **2II**. Intramolecular ring closure in a stereochemical determining step affords **2III**. Subsequent workup affords product **2a**. To demonstrate that the hydrogen

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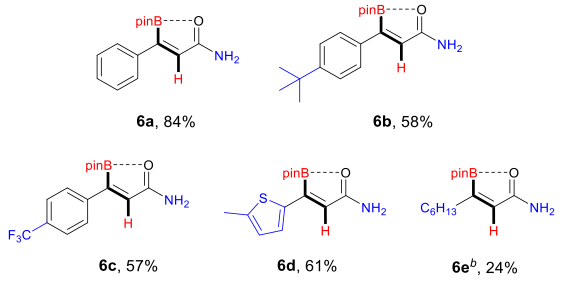
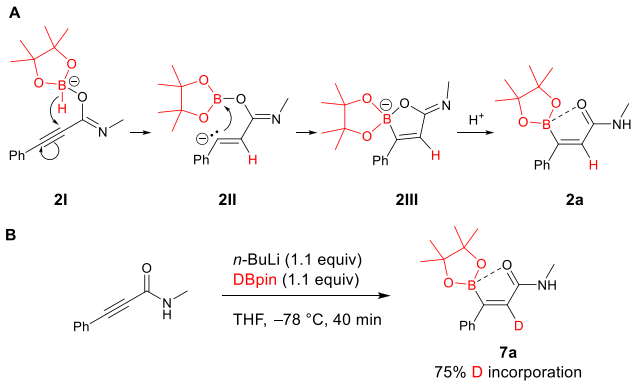
Scheme 4. Substrate Scope of Primary Propiolamides[a]



[a]General procedure: propiolamide (0.11 mmol) was diluted in THF (0.1 M); *n*-butyllithium (0.24 mmol, 2.5 M in hexanes) was added at −78 °C; pinacolborane (0.24 mmol) was added dropwise, and then the reaction was warmed to rt. [b]After reaching rt, the reaction was heated to 66 °C for 1.5 h.

Scheme 5. Plausible Mechanism and Deuterium Incorporation Study



on the α-carbon of the product is derived from pinacolborane, we performed a deuterium labeling utilizing deuteropinacolborane (see Scheme 5B). Compound **7a** indicated 75% deuterium incorporation, suggesting mechanistically that a formal hydroboration is occurring.

In conclusion, we have developed an efficient and stereoselective transition metal-free *trans*-hydroboration of primary and secondary propiolamides affording the corresponding (*E*)-β-borylacrylamides. A wide substrate scope was demonstrated with a variety of aromatic, heteroaromatic, and aliphatic propiolamides. This protocol provides a method for these otherwise inaccessible commodity materials. Further investigations into the synthetic and medicinal applications of the borylated products is an ongoing area of research, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02408.

Experimental procedures and NMR data (PDF)

Accession Codes

CCDC 1907775, 1907776, 1907777, 1907778, and 1907779 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) Note that use of crown ether was necessary for the efficient diboration and silaboration of alkynamides; see refs 14 and 15.

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