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

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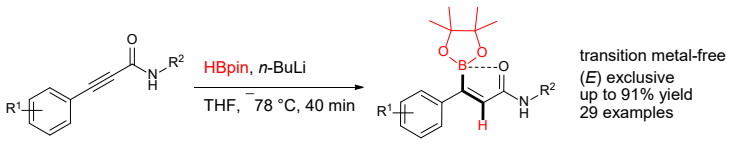
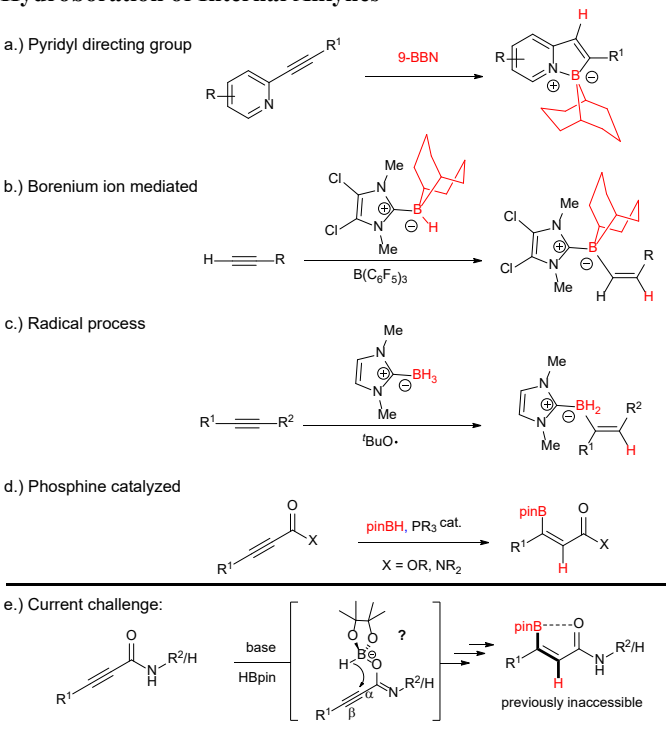
Supporting Information Placeholder



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 regio- 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 is discussed involving substrate-assisted activation and a key intramolecular cyclization.

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 carbon-carbon triple bonds using trivalent borane reagents generate organoboron compounds with *cis* configuration;[3] the resulting alkenylboronates are particularly advantageous due to 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 (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 regio- 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 regio- and stereoselectivity was observed acro-ss 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, Sawamura, and Vilotijevic

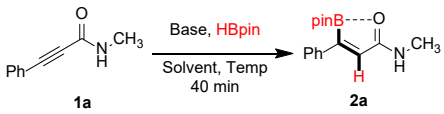
Scheme 1. Strategies for the Transition Metal-Free *trans*-Hydroboration of Internal Alkynes



(Scheme 1d).[12] The hydroboration reaction proceeded under mild conditions with less than 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 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 regio- 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[16] methodology reported by Uchiyama (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]

Table 1. Optimization of Reaction Conditions[a]



Entry	Solvent	Base/Catalyst (equiv)	Temp (ºC)	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 ºC. Pinacolborane (0.22 mmol) was added dropwise then the reaction was warmed to 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: cyclopentylmethylether; DCM: dichloromethane.

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*-BuLi (1.4 equiv) in the presence of 12-crown-4 and HBpin at –78 ºC to afford **2a** in good yield (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 towards HBpin. Reducing the equivalency of reagents resulted in a minor increase in yield (entry 3), but diluting the reaction mixture further increased the product yield (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 (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 (entry 6). Alternative bases such as phenyllithium also efficiently mediated the transformation, albeit in slightly lower yield (entry 7). The use of a Grignard reagent such as EtMgBr resulted in an unsatisfactory yield (entry 8). Unfortunately, metal hydrides such as LiH do not mediate the hydroboration reaction, although the reason for this is unclear (entry 9). We found that LiTMP and LDA also afforded **2a**, but at the cost off a modest reduction in yield (entries 10 and 11). Weaker bases such as *t*-BuOLi or TEA were ineffective (entries 12 and 13). We next determined the effect of solvents. Replacing THF with toluene or CPME resulted in poor yields likely due to reduced solubility of ionic intermediates (entries 14 and 15). Dichloromethane as a solvent afforded **2a** in only a modest yield (entry 16). We thus chose *n*-BuLi as the base with THF as solvent as the optimized reaction condition (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 #1907779).

With the optimal reaction conditions in hand, we sought to determine the substrate scope and limitations (Scheme 2). Increasing 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. Further, 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

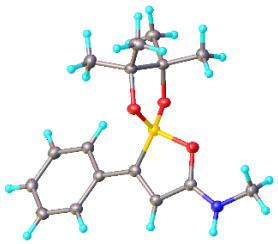
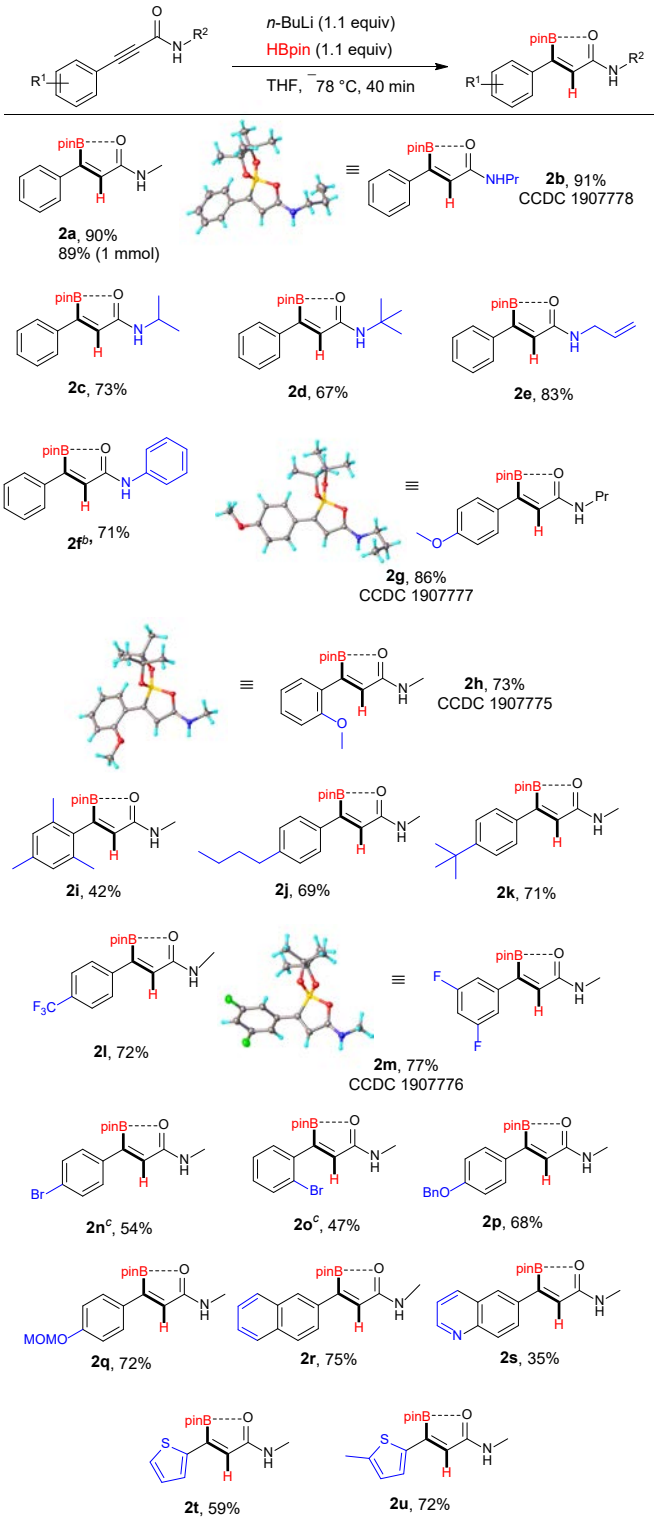


Figure 1. X-ray crystal structure of compound **2a** (CCDC 1907779, see Supporting Information)

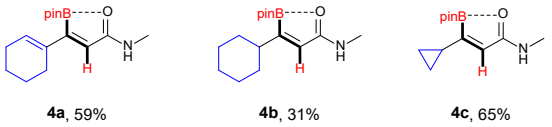
also well tolerated. Aryl substituents with electron donating groups such as 4-methoxyphenyl (**1g**) and 2-methoxyphenyl (**1h**) substituted propiolamides efficiently afforded **2g** and **2h** in excellent yields. Alkyl substituents on the ring (**1i**–**1k**) were efficient substrates, although increasing steric bulk such as in

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 ºC. *n*-Butyllithium (0.275 mmol, 2.5 M in hexanes) was added at –78 ºC followed by pinacolborane (0.275 mmol), then the reaction was warmed to rt. [b]Performed with PhLi. [c]Performed with LiTMP.

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



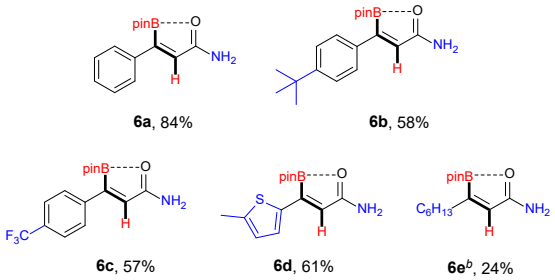
[a]General procedure: Same as in Scheme 1. After reaching rt, these reactions were heated to 66 ºC for 1.5 h.

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 sub strates 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 like quinoline **1s** as well as thiophenes **1t**–**u** 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 the 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% of isolated product (Scheme 2).

With the substrate scope of aryl substituents established, we determined the tolerance of the reaction with non-aromatic 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]

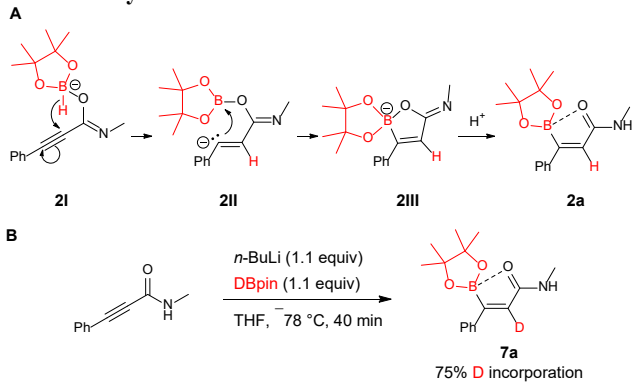
Primary amides are specially challenging for alkyne reduction as, to date, limited examples exist for this transformation.[14-15] Utilizing the developed method with 2 equiv of *n*-BuLi and pinacolborane, 3-phenylpropiolamide (**5a**) was borylated in excellent yield (Scheme 4). Other functional groups on the phenyl ring such as electron donating methyl (**6b**) and electron withdrawing trifluoromethyl (**6c**) were likewise generated in good

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 ºC. Pinacolborane (0.24 mmol) was added dropwise then the reaction was warmed to rt. [b]After reaching rt, the reaction was heated to 66 ºC for 1.5 h.

Scheme 5. Plausible Mechanism and Deuterium Incorporation Study.



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 addition of pinacolborane likely lead 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 work-up affords product **2a**. To demonstrate that the hydrogen on the α-carbon of the product is derived from pi-nacolborane, we performed a deuterium labeling utilizing deuteropinacolborane (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.

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