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Phosphine-catalyzed Hydroboration of Propiolonitriles: Access to (*E*)-1,2-vinylcyanotrifluoroborate derivatives

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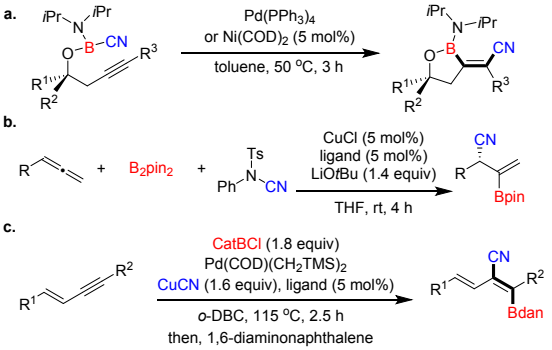
We report an organocatalytic *trans* hydroboration of 3-substituted-propiolonitriles. In the presence of catalytic amounts of tributylphosphine and pinacolborane, regioselective hydroboration of the internal triple bond proceeded in a stereoselective fashion under mild conditions to afford the corresponding (*E*)-1,2-vinylcyanoborane derivatives. The mechanism is proposed to occur through a 1,2-phosphine addition instead of a canonical 1,4-conjugate addition pathway.

Organoboron compounds are widely utilized in organic synthesis and the boronic acid functional group is among the most versatile in chemical transformations.[1] The Suzuki-Miyaura cross-coupling reaction has employed these substrates for otherwise difficult carbon-carbon bond formations with alkenylboronates particularly successful.[2] Therefore, methods for synthesizing functionalized alkenylboronates continue to be a subject of intense investigation. The alkenyl nitrile functional moiety plays a vital role in several FDA-approved drugs, polymer science, and as intermediates in commodity chemicals.[3] Fortunately, several transition metal-catalyzed (Pd, Ni, Fe, Ga, Cu, Rh, *etc*) preparations of substituted α,β-unsaturated nitriles have been reported.[4] Alkenyl nitriles bearing amine, triflate, chlorine, silicon, sulfur, germanium, and tin have been synthesized from alkynes.[5] In seminal work by Suginome and co-workers, borylacrylonitriles were accessed using palladium and nickel catalysts through intramolecular cyanoboration (Scheme 1a).[6] Intermolecular reactions to achieve such products have included copper-catalyzed cyanoboration of allenes using electrophilic cyanation agent, N-cyano-N-phenyl-p-toluenesulfonamide, and bis(pinacolato)diboron (B_2pin_2) (Scheme 1b).[7] Interestingly, Liu and co-workers reported a palladium-catalyzed, *trans* selective cyanoboration of enynes



Scheme 1 Approaches to 1,2-vinylcyanoborane derivatives. *o*-DBC: 1,2-dichlorobenzene, Bdan: 1,8-diaminonaphthyl boronate

using a 1,4-azaborine-based Senphos ligand (Scheme 1c).[8]

While these methods are effective, transition metals and specialized reagents are required. Furthermore, the use of toxic cyanating reagents and generation of hydrogen cyanide make some of these reactions unappealing. Thus, alternative methods towards the synthesis of cyano and boron containing compounds are of interest.[9]

Recently, phosphine catalysts have been employed in transition metal free *trans*-selective borylation reactions of polarized alkynes.[10] Work by Sawamura and Vilotijevic as well as our laboratory suggest a mechanism involving a 1,4-conjugate addition of the phosphine to produce an allenolate Lewis acid-base complex that facilitates intramolecular hydride transfer to the central carbon (Scheme 2a).[11] In contrast, hydroboration of alkynylnitriles could result in the reduction of the nitrile to the imine or amine as well as the alkyne to the alkene (Scheme 2b).[12] Notwithstanding chemo- and stereoselectivity issues, six products can potentially be formed. Herein, we report the first transition metal-free synthesis of 1,2-vinylcyanoborane derivatives via an (*E*)-selective hydroboration of propiolonitriles. In contrast to the hydroboration mechanism in Scheme 2a, 1,4-conjugate addition to alkynylnitrile generates

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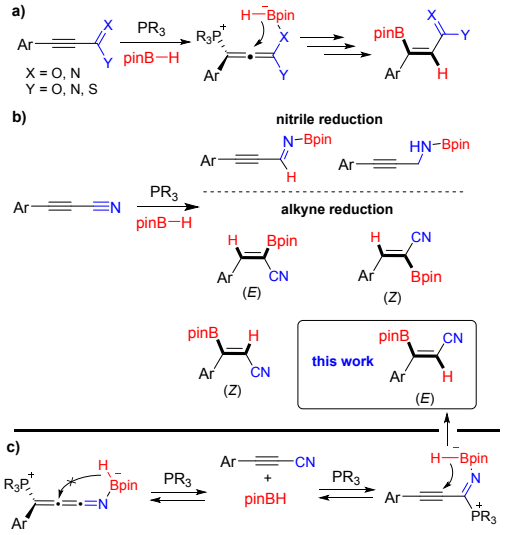
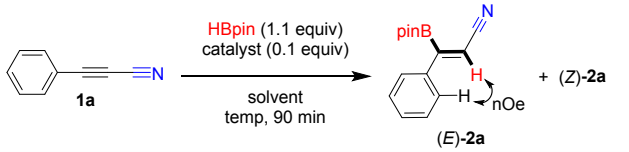


Scheme 2 Hydroboration of polarized alkynes.

a BN-cumulene complex that is incompetent to undergo internal hydride transfer (Scheme 2c). Instead, the phosphine adds in a 1,2-fashion to generate a BN-imine intermediate that is poised for hydride transfer to the α-carbon forming the desired (*E*)-1,2-vinylcyanoborons.

We initiated our studies by reacting 3-phenylpropiolonitrile (**1a**) with pinacolborane in the presence of a tributylphosphine catalyst with dichloromethane as the reaction solvent (Table 1, entry 1). Fortunately, compound **2** was formed in 96% yield and 90:10 (*E*:*Z*) selectivity. Further investigation revealed that a phosphine catalyst is required for the reaction to proceed (entry 2). This was supported by the lack of product formation when tributylphosphine was replaced with a base typically used for borylation reactions such as KO*t*Bu (entry 3). Trimethylphosphine and tricyclohexylphosphine successfully catalyzed the hydroboration reaction with reduced yield and selectivity while triphenylphosphine afforded only a trace amount of the 1,2-vinylcyanoborane product (entries 4-6). The less nucleophilic triphenylphosphine relative to other phosphines likely reduced efficiency of addition to the nitrile carbon. Increasing the equivalency of pinacolborane had no impact on product yield but did demonstrate a slight reduction in selectivity (entries 7-8). Performing the reaction in THF and toluene gave reductions in both yield and selectivity, while DMF resulted in minimal product formation (entries 9-11). While acetonitrile slightly improved reaction selectivity, the yield decreased (entry 12). We then investigated the effect of temperature on selectivity. Performing the reaction at 40 °C resulted in a reduction of both yield and *E*:*Z* ratio (entry 13). However, a reaction temperature of 0 °C increased selectivity to 93:7 (*E*:*Z*) (entry 14). Thus, the reaction was further cooled, and dichloromethane was used as the solvent. To our delight, conducting the reaction at –40 °C followed by slow warming to rt afforded **2a** in 96:4 (*E*:*Z*) selectivity and reasonable yield (entry 15). Therefore, entry 15 was selected as the optimized set of reaction conditions. The stereochemistry of the (*E*)-**2a** was established by nuclear Overhauser effect studies (Table 1).

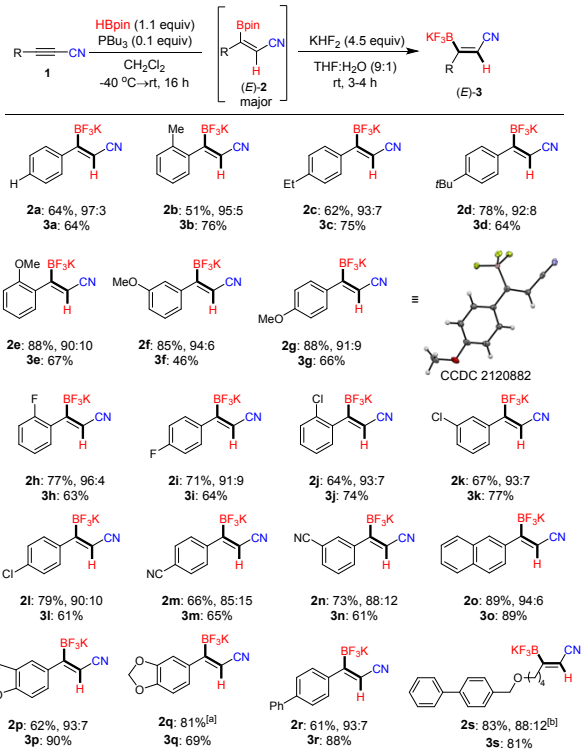
Table 1 Optimization of Reaction Conditions.[a]



entry	solvent	catalyst	temp (°C)	yield [b]	*E*:*Z* [b]
1	CH_2Cl_2	PBu_3	rt	96	90:10
2	CH_2Cl_2	None	rt	0	-
3	CH_2Cl_2	KO*t*Bu	rt	0	-
4	CH_2Cl_2	PMe_3	rt	87	85:15
5	CH_2Cl_2	PCy_3	rt	75	89:11
6	CH_2Cl_2	PPh_3	rt	trace	58:42
7[c]	CH_2Cl_2	PBu_3	rt	96	89:11
8[d]	CH_2Cl_2	PBu_3	rt	96	88:12
9	THF	PBu_3	rt	70	85:15
10	toluene	PBu_3	rt	83	89:11
11	DMF	PBu_3	rt	trace	87:13
12	MeCN	PBu_3	rt	85	91:9
13	MeCN	PBu_3	40	54	89:11
14[e]	MeCN	PBu_3	0	66	93:7
15[f][g][h]	CH_2Cl_2	PBu_3	–40-rt	62	96:4
16[f]	CH_2Cl_2	PPh_3	rt	58	72:28

[a] 3-phenylpropiolonitrile (0.39 mmol) and pinacolborane (0.43 mmol) in solvent (0.3 M), catalyst (0.039 mmol). [b] Determined by ^{1}H NMR. [c] 1.5 equiv HBpin. [d] 2.2 equiv HBpin. [e] 3 h. [f] 16 h [g] 1.0 equiv HBpin afforded 50% yield and 93:7 *E*:*Z*. [h] 0.2 equiv PBu_3 afforded 62% yield and 93:7 *E*:*Z*.

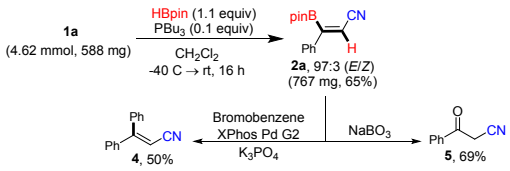
With these conditions in hand, the substrate scope was investigated. For these studies, we determined the stereoselectivity of the reaction by ^{1}H NMR of the crude reaction mixture, and for ease of isolation, the pinacolboronate esters (**2**) were converted to the corresponding potassium trifluoroborate salts (**3**) using potassium hydrogen difluoride in a mixture of THF and water (Scheme 3). In all cases, only the (*E*)-isomer crystallized. Thus, aryl rings bearing alkyl substituents such as 2-methyl (**1b**), 4-ethyl (**1c**), and 4-*tert*-butyl (**1d**) were tolerated, affording up to 95:5 (*E*:*Z*) selectivity and 78% yield of the corresponding 1,2-vinylcyanotrifluoroborate salts **3b**-**3d**. Electron donating groups such as methoxy in *ortho* (**3e**), *meta* (**3f**), and *para* (**3g**) positions resulted in good yields, albeit with slightly reduced selectivity. Fortunately, potassium 1,2-vinylcyanotrifluoroborate **3g** (CCDC 2120882)[13] afforded single crystals suitable for X-ray crystallography. The molecular structure of **3g** unambiguously corroborates the *E* geometry of the alkene moiety consistent with **2a**. We next investigated electron withdrawing groups on the phenyl ring such as fluoro (**3h**-**3i**) and chloro (**3j**-**3l**), and these groups were well tolerated. We were gratified to observe that despite a slight reduction in selectivity, substrates containing an additional cyano group either on the *meta* or *para* position were successfully transformed to the corresponding 1,2-vinylcyanotrifluoroborate products **3m** and **3n**. Next, we determined the effect of larger aromatic rings as well as



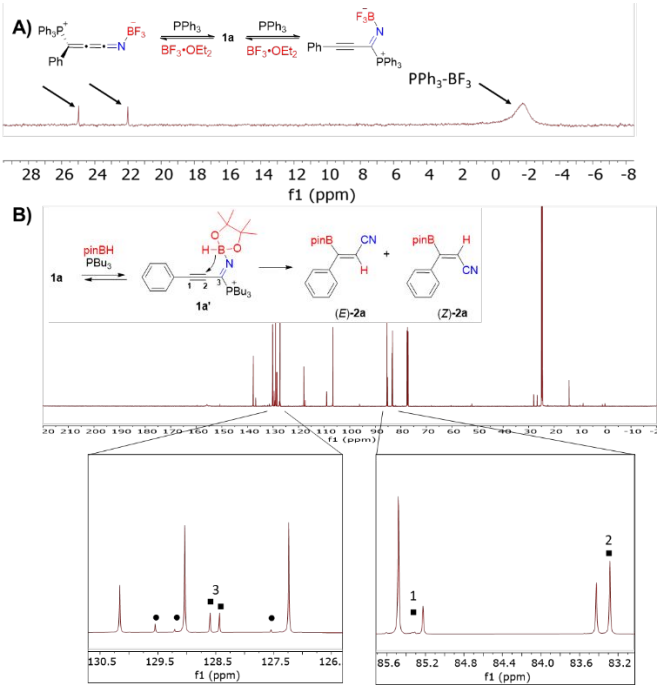
Scheme 3 Substrate scope. General procedure: 3-aryl/alkylpropionitrile (0.39 mmol) and pinacolborane (0.43 mmol) in CH_2Cl_2 was cooled to –40°C. After addition of PBu_3 (0.039 mmol), the mixture was slowly warmed to rt. The resulting boronic ester was treated with KHF_2 in THF:H_2O (9:1) for 2 h. Yields and *E*/*Z* ratios of **2a**-**2r** are from ^{1}H NMR. The isolated trifluoroborate **3a**-**3r** yields are from boron pinacol ester intermediates **2**. [a] Due to overlapping ^{1}H NMR signals, the *E*:*Z* ratio could not be determined. [b] Isolated as a 90:10 mixture of E/Z isomers.

heterocyclic ring systems. Naphthyl (**1o**), benzofuranyl (**1p**), benzo[*d*][1,3]dioxole (**1q**), and biphenyl (**1r**) substrates were successfully converted to the corresponding(*E*)-1,2-vinylcyanotrifluoroborate salts (**3o**-**3r**) in up to 90% yield.

Finally, the alkyl propiolonitrile **2s** was successfully converted to the corresponding 1,2-vinylcyanotrifluoroborate salt (**3s**). To demonstrate the scalability, we performed a 4.62 mmol scale reaction using **1a** and isolated the corresponding borylated product **2a** in 65% yield as a 97:3 mixture of *E*/*Z* isomers, which was identical to what was observed during the substrate scope studies (Scheme 4). With the scope and limitation established, we evaluated their synthetic transformations. Suzuki-Miyaura cross-coupling of **2a** with bromobenzene using XPhos Pd G2 as a catalyst produced **4** in 50% yield. Additionally, compound **2a** was successfully oxidized with sodium perborate to afford the corresponding β-ketonitrile **5** in 69% yield. β-ketonitriles are important precursors for the synthesis of various heterocycles including



Scheme 4 Large scale synthesis and application of **2a**.



Scheme 5 A) ^{31}P NMR studies in chloroform. PPh_3 (80 µmol), BF_3·OEt_2 (80 µmol), and **1a** (80 µmol). **B)** ^{13}C NMR studies in chloroform at -20 °C. PBu_3 (0.039 mmol), pinacolborane (0.43 mmol), and **1a** (0.39 mmol). New peaks appeared that correspond to the alkyne (▪) and aryl (•) carbons of intermediate **1a'**. Unlabelled peaks are either from starting materials or **2a**. Reference spectra of **1a** and (*E*)-**2a** are provided in the Supplementary Information.

aminopyrazoles, aminoisoxazoles, 2-pyridones, and imidazoles.[14]

As shown in Scheme 2c, tributyl phosphine likely undergoes a reversible 1,4- and 1,2-conjugate addition to propiolonitrile **1a**. To monitor both species, we performed ^{31}P NMR studies. For this purpose, PPh_3 was used as the reaction occurs rapidly with PBu_3. Table 1 (entry 16) indicates PPh_3 as an efficient catalyst that affords the product **2a** in 58% yield albeit at elevated temperature and decreased stereoselectivity. As shown in Scheme 5a, the combination of **2a**, PPh_3, and BF_3·OEt_2 (HBpin surrogate) resulted in the appearance of two new peaks at 22 and 25 ppm, which is consistent with vinyl and acyl phosphoniums.[15] Furthermore, we performed a ^{13}C NMR experiment with **1a** in the presence of tributylphosphine and pinacolborane at -20 °C and, after 30 mins of the reaction, two new peaks at 83 and 85 ppm as well as a doublet (J = 24 Hz) at 128 ppm appeared that we tentatively assign to the alkyne and imine phosphonium carbons, respectively (Scheme 5b). Taken together, these results suggest the formation of a BN-imine-phosphonium intermediate **1a'**. Thus, a proposed mechanism is illustrated in Scheme 6. Lewis acid-base complexation generates a sufficiently activated nitrile that is susceptible to 1,2-addition with phosphine to form iminophosphonium intermediate **A** that transfers a hydride to the α-carbon to produce **B**. C-C bond rotation aligns the vinyl anion and Bpin to allow a 1,4-borotopic transfer via 5 membered heterocycle **D**. Elimination of PBu_3 produces (*E*)-**2a**.

In conclusion, we developed a transition metal-free *trans* selective hydroboration of propiolonitriles using

tributylphosphine as a catalyst. The reaction is simple, tolerates a wide variety of substrates, and selectively affords (*E*)-1,2-vinylcyanotrifluoroborate salts in good yield and stereoselectivity. The reaction is proposed to proceed following a 1,2-addition of phosphine instead of the canonical 1,4-addition pathway.

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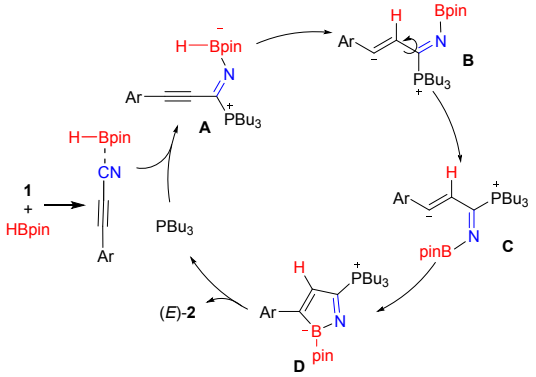

Scheme 6 Proposed mechanism.

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