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Carboxylic Acid-Catalyzed Highly Efficient and Selective Hydroboration of Alkynes with Pinacolborane

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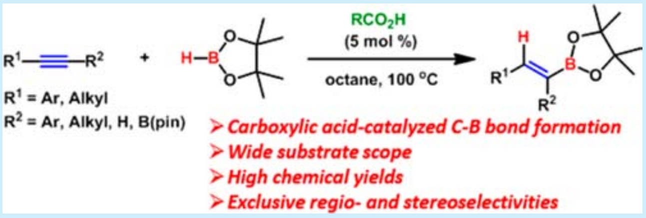
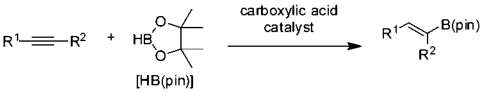
Supporting Information

ABSTRACT: We have demonstrated for the first time that carboxylic acids are able to catalyze the direct hydroboration of various terminal and internal alkynes with pinacolborane without using any metal catalysts. This unprecedented catalytic hydroboration exhibits a broad functional groups compatibility, giving the corresponding alkenyl diboronates and monoboronates in good to high yields with exclusive regio- and stereoselectivities.



It is well-known that the C−B bond of organoboranes is cleaved through C−B bond protonolysis with carboxylic acids.[1] It has believed for a long time that carboxylic acids are reagents for C−B bond cleavage. Quite surprisingly, we have found that carboxylic acids catalyze hydroboration of alkynes with pinacolborane [HB(pin)], giving the alkenylboranes in good to high yields with exclusive regio- and stereoselectivities (eq 1).



(1)

The direct hydroboration of alkynes is one of the most powerful and straightforward methods to form the alkenylboronates, which are important synthetic intermediates in various useful transformations,[2,3] such as Pd-catalyzed Suzuki−Miyaura cross-coupling to construct complex molecules for useful organic semiconductors and pharmaceuticals. During the last five decades, diverse alkyne−hydroboration reactions, including uncatalyzed,[4] metal-catalyzed,[2b,5] and base-catalyzed,[6] have been developed using various hydroborating reagents. Among them, the hydroboration of alkynes with HB(pin) or bis(pinacolato)diboron [$B_2(pin)_2$] by using transition-metal catalysts has been extensively studied in an effort to improve the efficiency and selectivity of the resulting alkenyl pinacolboronate esters, which are highly dependent on the catalyst species, ligands, base additives, and alkyne structures.[5] The alkenyl pinacolboronate esters have been found to exhibit excellent thermal stability and air- and water-insensitivity, which can be purified by aqueous workup and silica chromatography.[2b]

The selective synthesis of 1,1-diborylalkenes is particularly attractive because they enable the construction of useful π-conjugated molecules through the Pd-catalyzed multiple carbon−carbon formation.[7] In spite of their important synthetic utility, the direct hydroboration of alkynylboronates with organoborane to the corresponding 1,1-diborylalkenes has never been explored.[8] This class of compounds has been prepared by Hiyama and co-workers using 1-halo-1-lithioalkenes and $B_2(Pin)_2$.[9] The research groups of Marder and Iwasawa reported independently the catalytic dehydrogenative borylation of alkenes with $B_2(Pin)_2$ using rhodium and Pd-pincer complexes.[10] In this paper, we began our investigation by using alkynylboronates and HB(pin) to realize a new and direct hydroboration for synthesis of 1,1-diborylalkenes without using metal catalysts.

Initially, a variety of organocatalysts have been screened in the hydroboration of 2-phenyl-1-ethynylboronic acid pinacol ester (**1a**) with HB(pin) (5 equiv) as a boron source in octane at 100 °C for 12 h. In the absence of catalysts, the reaction was sluggish without producing the desired 1,1-diborylalkene product **2a** (Table 1, entry 1). Surprisingly, the reaction proceeded smoothly in the presence of a catalytic amount of acetic acid to afford **2a** in high yield with an exclusive regioselectivity (entry 2). This unusual result led us to further examine various carboxylic acids and their analogues. Formic acid exhibits almost the same catalytic activity as acetic acid, while the sterically hindered pivalic acid and 2,2,2-triphenylacetic acid and rather strong acid such as trifluoroacetic acid decreased the yield of **2a** (entries 3−6). The use of triflic acid, one of the strongest Brønsted acids, resulted in decomposition of **1a** without yielding **2a** (entry 7). We were pleased to find that benzoic acid catalyzed the hydroboration reaction efficiently to give **2a** in almost quantitative yield (entry 8).

In order to figure out the relationship between chemical yield and acidity of carboxylic acid catalysts,[11] various benzoic acids bearing different functional groups have been studied. The use of benzoic acids having electron-withdrawing groups of nitro or

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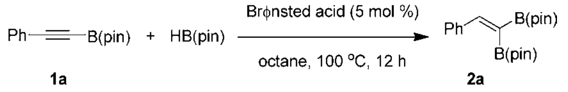
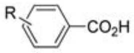
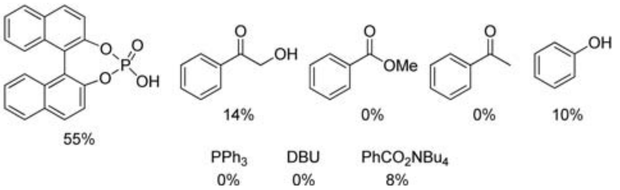
Table 1. Screening of Various Organocatalysts for Hydroboration of 2-Phenyl-1-ethynylboronic Acid Pinacol Ester (1a) with HB(pin)[a]



entry	catalyst (pKa)[b]	yield (%)[c]
1	none	0
2	AcOH (4.76)	94
3	HCO_2H (3.75)	85
4	PivOH (5.03)	79
5	$(Ph)_3CCO_2H$	79
6	CF_3CO_2H (0.52)	83
7	TfOH	0
8	$PhCO_2H$ (4.20)	99 (94)
		
9	R = 4-NO_2 (3.44)	72
10	R = 4-Ac	85
11	R = 4-Me (4.34)	99
12	R = 4-OMe (4.47)	99
13	R = 4-NMe_2 (5.03)	99 (94)[d]
14	R = 2-NMe_2 (8.42)	0
15	R = 2-C_6H_5 (3.46)	80

other organocatalysts:



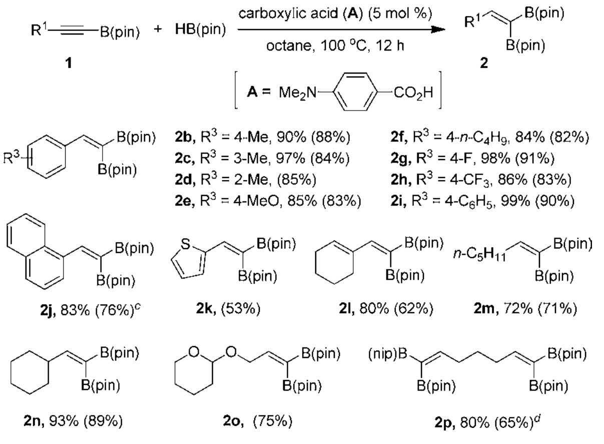
[a]Reaction conditions: **1a** (0.4 mmol), HB(pin) (2 mmol), catalyst (5 mol %), octane (1 M), 100 °C for 12 h under an argon atmosphere. [b]Thermodynamic pK_a values according to ref 11. [c]The ^{1}H NMR yield of **2a** determined using CH_2Br_2 as an internal standard. Isolated yields are shown in parentheses. [d]The reaction was carried out for 8 h.

acyl on the benzene ring resulted in substantially diminished yield of **2a** (entries 9 and 10). On the contrary, benzoic acids with an electron-donating group at the *para*-position of the benzene ring showed a remarkably high catalytic activity. For example, the use of 4-methyl-, 4-methoxy-, and 4-(dimethylamino)-substituted benzoic acids as catalysts, respectively, resulted in a quantitative yield of the corresponding product **2a** being obtained (entries 11–13). Among them, 4-(dimethylamino)benzoic acid having a strong electron-donating group exhibited the highest catalytic activity, furnishing **2a** within 8 h (entry 13). These results showed a clear trend that the chemical yield roughly depends on the acidity of carboxylic acids; weaker aromatic carboxylic acids give higher chemical yields (entries 8–13). It is worth noting that the totally different catalytic activity between 2-(dimethylamino)benzoic acid (0%) and (1,1′-biphenyl)-2-carboxylic acid (80%) indicates that the chelation of 2-dimethylamino group to boron may form a stable, inactive four-coordinate boron species bound to N and O atoms of benzoic acid (entries 14 and 15). It was noted that we did not observe any reduced compounds of carboxylic acids under the reaction conditions.

Organic phosphoric acid also can be used as a Brønsted acid catalyst; the yield of **2a** (55%) is lower than that of carboxylic acids (Table 1). Other organocatalysts without a carboxylic acid group, such as 2-hydroxy-1-phenylethanone, methyl benzoate, acetophenone, phenol, and triphenylphosphine, were found to be ineffective in catalyzing the present hydroboration (Table 1). The results indicate that the carboxylic group is essentially crucial for catalytic hydroboration of alkynes with HB(pin). Additionally, the solvent examination revealed that the use of nonpolar solvents is preferred for obtaining high yields of **2a**, and the polar solvents, such as dichloroethane, tetrahydrofuran, acetonitrile, ethyl acetate, and 1,4-dioxane afforded **2a** in low yields of 20–40% (Table S2, Supporting Information). Other hydroborating reagents, 9-BBN and HB(cat), are incompatible with the present reaction conditions, which resulted in a complex mixture of products. Finally, it should be noted that the use of lesser amounts of HB(pin) (3 equiv) resulted in a decreased yield of **2a** (75%) due to the consumption of HB(pin) by water under the present conditions leading to the formation of HOB(pin) and [(pin)B]$_2$O. Overall, the use of 4-(dimethylamino)benzoic acid as a catalyst in octane was chosen as the optimal conditions for regio- and stereoselective hydroboration of alkynes with HB(pin).

To explore the generality and scope of this method, various alkynylboronates were examined under the optimized conditions. All products were isolated using Kugelrohr distillation to remove low boiling point compounds, followed by a short silica gel column chromatography. It should be mentioned that the hydroboration of every alkyne employed in the present work almost did not proceed in the absence of catalysts. As shown in Scheme 1, a wide range of functional group tolerance and an exclusive regioselectivity were observed. The reactions of 2-(tolyl)ethynylboronates having an electron-donating methyl group at the phenyl ring proceeded efficiently to afford the corresponding 1,1-diborylalkenes **2b–d** in high yields

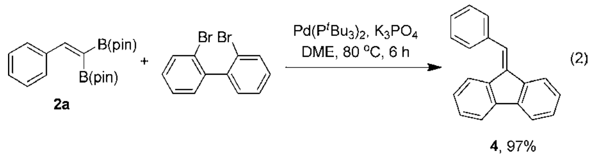
Scheme 1. Carboxylic Acid Catalyzed Hydroboration of Various Alkynylboronates (1) with HB(pin)[a,b]



[a]Reaction conditions: **1** (0.4 mmol), HB(pin) (2 mmol), 4-(dimethylamino)benzoic acid (5 mol %), octane (1 M, 0.4 mL), Ar atmosphere, 100 °C, 12 h. [b]^{1}H NMR yield determined using CH_2Br_2 as an internal standard. Isolated yields are shown in parentheses. [c]The reaction temperature for **2j** is 120 °C and reaction time is 8 h. [d]The reaction for forming **2p** carried out at 120 °C for 12 h using 10 equiv of HB(pin).

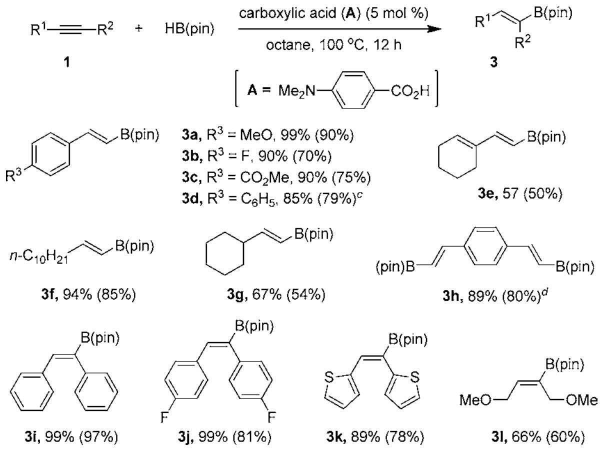
regardless of the position of methyl substituent. The reactions of arylalkynes bearing electron-donating and electron-withdrawing groups at the phenyl ring did not exhibit a large difference to the reaction outcome. For example, arylalkynylboronates having methoxyl, *n*-butyl, fluorine, and trifluoromethyl groups at R^1 produced the desired products **2e−h** in good to high yields. Alkynylboronates having biphenyl and naphthyl groups at the alkynyl terminus also worked uneventfully to afford **2i** and **2j** in high yields. 2-Thienyl alkynylboronate suffered from decomposition of the starting material together with a small amount of the semihydrogenated alkenylboronate, which lowered the yield of **2k** to 53%. The cyclohexenyl-substituted conjugated enynylboronate was also compatible with the acid-catalyzed conditions, in which the trisubstituted alkene moiety remained intact (**2l**). Likewise, the aliphatic alkynylboronates substituted with *n*-pentyl and cyclohexyl groups and tertahydropyran-protected propargyl alcohol were also good substrates to give the corresponding products **2m−o** in good to high isolated yields. The double hydroboration also took place when 1,6-diynylboronate was used as a substrate to give the corresponding tetraboryl diene **2p** in a 65% isolated yield. Other alkynylboronate such as 5,5-dimethyl-2-(phenylethynyl)-1,3,2-dioxaborinane failed to give the corresponding diboryl alkene, resulting in decomposition of the starting material due to its low stability under the standard conditions (Scheme S1, Supporting Information).

The resulting 1,1-diborylalkenes are synthetically useful substrates for further functionalization by Suzuki−Miyaura coupling. Thus, following the method developed by Shimizu and Hiyama et al.,[7] 1,1-diborylalkene **2a** was treated with 2,2′-dibromo-1,1′-biphenyl in the presence of Pd catalyst, which gave the corresponding product 9-benzylidene-9*H*-fluorene **4** in 97% yield through the double cross-coupling annulation (eq 2).



This method was further extended to the hydroboration of common alkynes (Scheme 2). To our delight, both terminal and internal alkynes were well tolerated to give monoboryl alkenes in good to high yields. Remarkably, this hydroboration proceeded through a perfect *anti*-Markovnikov and exclusive *syn*-addition of HB(pin) to alkynes. The reaction with terminal arylalkynes having electron-donating and electron-withdrawing groups, such as methoxy, fluorine, and ester groups at the phenyl ring produced the desired *E*-isomers **3a−c** exclusively, in which the methoxy-substituted electron-rich alkyne exhibited a better reactivity, giving **3a** in a 90% isolated yield. Biphenyl terminal alkyne is also a rather reactive substrate, giving a high yield of alkenylboronate **3d** within 6 h. The reaction of the conjugated 1-ethynylcyclohex-1-ene exhibited an exclusive chemoselectivity to the C−C triple bond, affording the corresponding diene **3e** in moderate yield. The hydroboration with aliphatic terminal alkynes also proceeded smoothly, converting dodec-1-yne and ethynylcyclohexane to the corresponding alkenylboronates **3f** and **3g** in good to high yields. Terminal diyne such as 1,4-diethynylbenzene underwent double hydroboration to give the corresponding diboronate **3h** in a 80% isolated yield. The hydroboration of symmetric internal alkynes also took place uneventfully. 1,2-Diphenylethyne,1,2-bis(4-fluorophenyl)ethyne, 1,2-di(thiophen-2-yl)-ethyne, and 1,4-dimethoxybut-2-yne were selectively hydroborated under the standard conditions to give the corresponding *Z*-isomers **3i−l** in good to excellent yields.

Scheme 2. Carboxylic Acid-Catalyzed Common Alkynes with HB(pin)[a,b]



[a] Reaction conditions: **1** (0.4 mmol), HB(pin) (3 equiv), octane (0.4 mL), 4-(dimethylamino)benzoic acid (5 mol %), 100 °C, 12 h, Ar atmosphere. [b] ^{1}H NMR yield was determined using CH_2Br_2 as an internal standard. Isolated yields are shown in parentheses. [c] The reaction time for **3d** is 6 h. [d] HB(pin) (5 equiv) was used for the formation of **3h**.

In an early paper, Brown and co-workers reported that the reaction of propionic acid with sodium borohydride could produce hydrogen gas and $[EtCO_2BH_3]^-Na^+$ which is an effective hydroborating reagent.[12] Ganem et al. proposed that the catecholboronate ester should be a key intermediate for the reaction of carboxylic acids with amines to form amides in the presence of catecholborane, which has been demonstrated by the infrared absorption.[13] Most recently, Antilla and co-workers reported that organic phosphoric acid reacted with HB(cat) to generate hydrogen gas and phosphoryl catechol boronate, and the latter species was an effective hydroborating reagent for reduction of ketones.[14] Although it is not yet clear at the present time how carboxylic acids catalyze the hydroboration reaction of pinacolborane toward alkynes, the present finding provides a synthetically useful procedure of hydroboration.

In conclusion, we have demonstrated for the first time that the carboxylic acids catalyze the hydroboration of alkynes with HB(pin). The hydroboration takes place with various terminal and internal alkynes having a wide range of functional groups without using any metal catalysts and additives, affording the synthetically important alkenyl diboronates and monoboronates in good to high yields with exclusive regio- and stereoselectivities. This method not only provides an efficient and general approach for formation of alkenylboronates, but also may open a new avenue for hydroboration of versatile unsaturated C−C multiple bonds using organocatalysts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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