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Phosphine-Catalyzed *Anti*-Carboboration of Alkynoates with Alkyl-, Alkenyl-, and Arylboranes

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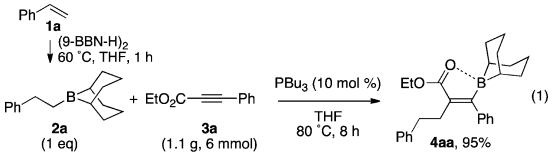
Supporting Information

ABSTRACT: We found that trialkylphosphine organocatalysts promoted unprecedented *anti*-carboboration of alkynoates with alkyl-, alkenyl-, or arylboranes to form β-boryl acrylates. The regioselectivity of the carboboration across the polar C−C triple bond exhibited inverse electronic demand, with the less electronegative B atom being delivered to the positively charged β carbon atom. The regioselectivity and the *anti* stereoselectivity were both complete and robust. In addition, the substrate scope was broad with excellent functional group compatibility.

Carboboration of internal alkynes with organoboron compounds offers an efficient strategy for the synthesis of trisubstituted alkenylboron derivatives, which can be utilized as precursors to tetrasubstituted alkenes.[1,2] Suginome and coworkers reported the palladium- and nickel-catalyzed carborations of internal alkynes with cyano-[1a−d] and alkynylboron[1e] derivatives. These reactions introduced carbon and boron atoms with *syn* stereochemistry. However, alkyne carboboration has not yet been expanded to the use of more common organoboron compounds such as alkyl-, alkenyl-, or arylboron compounds.[3] This is mainly due to resistance of the C−B bond in these compounds against oxidative addition to transition metals.[4]

In our study on metal-catalyzed transformations of organoboron compounds,[5] we unexpectedly found that an alkylborane (**2a**) reacted with an alkynoate (**3a**) in the presence of a catalytic amount of tributylphosphine (PBu_3) in a carboboration mode to give a β-boryl acrylate derivative (**4aa**) with a B−O coordination bond (eq 1).[6−8] Interestingly, the carboboration exhibited an



inverse electronic demand with regard to regioselectivity: the less electronegative B atom was introduced at the positively charged β carbon of the α,β-unsaturated ester (alkynoate), with the more electronegative C atom at the electron-neutral α carbon. To our knowledge, this mode of carboboration has not been reported. Another interesting feature of this reaction is the *anti* stereochemistry of the C−B bond addition. Both regio- and stereoselectivities are exclusive and robust irrespective of substrate structures. Although this study was mostly focused on the reaction of alkyl-9-BBN reagents (9-BBN: 9-borabicyclo[3.3.1]nonane) due to the convenience of their preparation, alkenyl or aryl-9-BBN reagents also worked as suitable substrates.

Specifically, a solution of alkylborane **2a** (6 mmol) was first prepared through hydroboration of styrene (**1a**) with a 9-borabicyclo[3.3.1]nonane dimer [$(9\text{-BBN-H})_2$] (3 mmol) in THF (24 mL) at 60 °C (**1a**/B 1.05:1). Subsequently, PBu_3 (10 mol %) and ethyl 3-phenylpropionate (**3a**) (1.1 g, 6 mmol) were added, and the mixture was heated at 80 °C over 8 h for complete conversion of **3a** (eq 1). Evaporation of volatiles followed by purification by recrystallization gave trisubstituted alkenylborane **4aa** in an isomerically pure form in 95% yield (based on **3a**). Single-crystal X-ray diffraction analysis of **4aa** confirmed that the alkyl group and the B atom were bound at the α and β positions of the alkynoate, respectively, and that the carbonyl oxygen coordinated to the boron atom (Figure 1). Thus, the C−B bond addition across the C−C triple bond was completely *anti*-stereoselective.

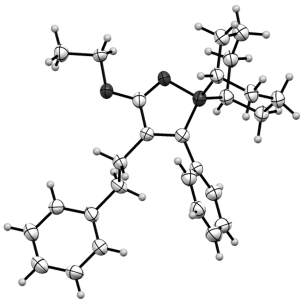


Figure 1. Molecular structure of **4aa** was confirmed by single-crystal X-ray diffraction analysis.

Presuming the role of PBu_3 as a nucleophilic catalyst,[9] we examined various potential nucleophiles as catalysts for the reaction between **2a** and **3a**, and PBu_3 was found to be the most effective (Table 1). The use of sterically less demanding PMe_3 or PEt_3 instead of PBu_3 under otherwise identical conditions resulted in significantly decreased substrate conversions and product yields (entries 3 and 4). Bulkier trialkylphosphines such as PCy_3 and P^tBu_3 were ineffective (entries 5 and 6). The weaker electron donors such as PPh_3 or $P(OPh)_3$ also resulted in no reaction (entries 7 and 8). DPPE or DCYPE bisphosphines showed slight catalytic activity (entries 9 and 10). These results can be summarized as follows. The electron-donating natures of

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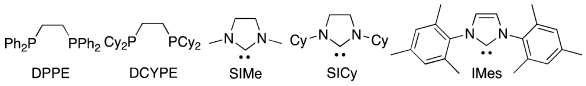
Table 1. Catalyst Effects in Carboboration of 3a with 2a[a]

entry	catalyst	yield (%)[b]
1	PBu_3 (eq 1)	99 (95)
2	PBu_3 (5 mol %)	99 (95)
3	PMe_3	48
4	PEt_3	29
5	PCy_3	0
6	P^tBu_3	0
7	PPh_3	0
8	$P(OPh)_3$	0
9	DPPE	9
10	DCYPE	7
11	SIMe	0
12	SICy	0
13	IMes	0
14	DABCO	0
15	DBU	0
16	DMAP	0
17	NBu_3	0

[a]Conditions of hydroboration: **1a**, 0.315 mmol; $(9\text{-BBN-H})_2$, 0.15 mmol (**1**/B 1.05:1); THF, 60 °C, 1 h. **2a** (0.3 mmol) was used without purification. Conditions of carboboration reaction: **3a**, 0.3 mmol; **2a**, 0.3 mmol; PBu_3, 10 mol %; THF, 80 °C, 8 h. [b]^{1}H NMR yield. Yield of the isolated product is in parentheses.



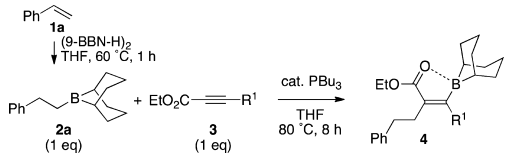
the P-alkyl substituents favored the phosphine catalysis, while bulkiness around the P center inhibited the reaction probably due to a decrease in nucleophilicity of the phosphine molecules. No reaction occurred with *N*-heterocyclic carbenes (NHCs) or amines (DABCO, DBU, DMAP, and NBu_3) with different steric and electronic natures (entries 11−17). The PBu_3 loading could be reduced to 5 mol % without affecting the yield of **4aa** (95%) (entry 2).

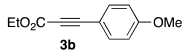
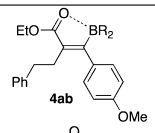
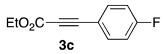
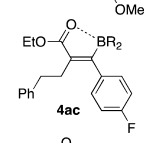
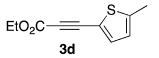
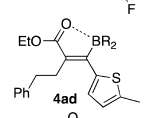
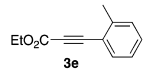
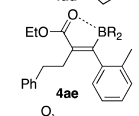
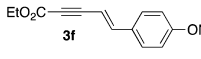
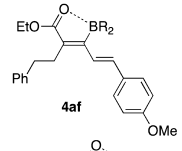
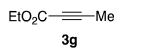
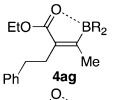
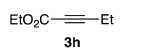
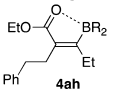
The use of (2-phenylethyl)boronic acid and its pinacolate ester instead of the alkyl-9-BBN reagents did not give the carboboration product at all, leaving both substrates almost unreacted. As alkynic substrates, the corresponding conjugated amides, aldehydes, or ketones as well as nonpolar internal alkenes showed no reactivity under similar conditions. The carboboration did not occur with C−C double bonds in conjugated enone or enoate derivatives.

Various alkynoates with different substituents at the β-position were subjected to the carboboration of **2a** with the PBu_3 catalyst (Table 2). Methoxy and fluoro groups were tolerated at the *para*-position of the aromatic β-substituent of the alkynoate (entries 1 and 2). The 2-thienyl-substituted alkynoate **3d** underwent the carboboration in high yield (entry 3). The reaction of the *o*-tolyl-substituted alkynoate **3e** proceeded at 100 °C (1,4-dioxane) with a 20 mol % catalyst loading to give a sterically congested alkenylborane (**4ae**) in moderate yield (entry 4).[10] The reaction of 1,3-enyne derivative **3f** occurred regioselectively to afford a conjugated 2,4-dienoate (**4af**) (entry 5).[10] The carboboration protocol was applicable to aliphatic alkynoates such as 2-butynoate (**3g**) and 2-pentynoate (**3h**) although the yields were lower than those from the reaction of the Ph-substituted alkynoate (**3a**) (entries 6 and 7).[10]

Various terminal alkenes were subjected to 9-BBN-hydroboration and were used for carboboration of **3a** (Table 3). The reaction tolerated functional groups such as chloro and methoxy

Table 2. Scope of Alkynoates[a]



entry	alkynoate	product	yield (%)[b]
1	 **3b**	 **4ab**	89
2	 **3c**	 **4ac**	91
3	 **3d**	 **4ad**	87
4[c]	 **3e**	 **4ae**	55
5	 **3f**	 **4af**	50
6	 **3g**	 **4ag**	62
7	 **3h**	 **4ah**	34

[a]Conditions of hydroboration: **1**, 0.315 mmol; $(9\text{-BBN-H})_2$, 0.15 mmol (**1**/B 1.05:1); THF, 60 °C, 1 h. **2a** (0.3 mmol) was used without purification. Conditions of carboboration reaction: **3**, 0.3 mmol; **2a**, 0.3 mmol; PBu_3, 10 mol % (entries 1−3, 5 and 6) or 20 mol % (entries 4 and 7); THF, 80 °C, 8 h. [b]Yield of the isolated product (silica gel chromatography). [c]Reaction was carried out in 1,4-dioxane at 100 °C.

groups on aromatic rings as well as acetal, phthalimide, ester, carbamate, and silyl ether moieties in aliphatic chains of alkylboranes (entries 1−8).

The tolerance toward steric demand in the alkylboranes (**2**) was also evaluated, and the results are shown in Table 3. The sterically more demanding alkylborane **2g**, which was derived from a terminal alkene **1g** bearing a tertiary alkyl substituent, served as a substrate to afford the corresponding product in high yield (entry 6). However, the use of secondary alkylborane **2j** prepared from cyclohexene resulted in low conversion and poor yield (entry 9).

Ethyl-9-BBN (**2k**), which was derived from hydroboration of ethylene (**1k**), was a suitable substrate (Table 3, entry 10). This reaction delivered an ethyl group to the α carbon atom of the alkynoate in high yield (87%). However, the carboboration with Et_3B (**5a**) resulted in a lower product yield (47%) (eq 2).

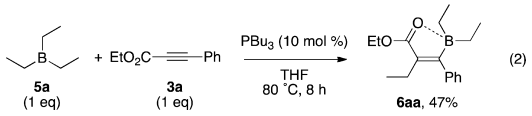


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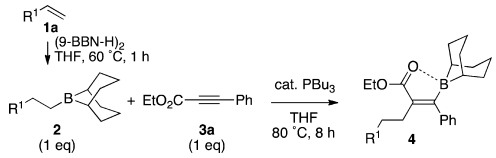
Table 3. Scope of Alkylboranes[a]



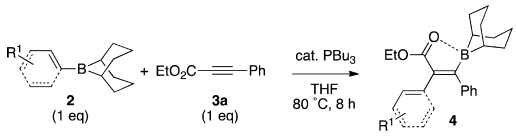
entry	alkene	product	yield (%)[b]
1	1b	4ba	87
2	1c	4ca	80
3	1d	4da	80
4	1e	4ea	87
5	1f	4fa	98
6	1g	4ga	96
7	1h	4ha	94
8	1i	4ia	96
9	1j	4ja	3
10	1k	4ka	87

[a]Conditions of hydroboration: **1**, 0.315 mmol; $(9\text{-BBN-H})_2$, 0.15 mmol (**1**/B 1.05:1); THF, 60 °C, 1 h. **2** (0.3 mmol) was used without purification. Conditions of carboboration reaction: **3a**, 0.3 mmol; **2**, 0.3 mmol; PBu_3, 10 mol %; THF, 80 °C, 8 h. [b]Yield of the isolated product (silica gel chromatography).

The phosphine-catalyzed carboboration was also possible with alkenyl- and arylboranes, allowing the introduction of sp^2 carbons to the α carbon atom of the alkynoate (Table 4). For instance, the carboboration with β-borylstyrene **2l**, which was prepared in advance through hydroboration of phenylacetylene (**1l**), occurred to afford the 1,3-dienylborane derivative **4la** (entry 1). Alkyl-substituted alkenylborane **2m** was also a suitable substrate (entry 2).

The reaction of phenyl-9-BBN (**2n**) with **3a** proceeded efficiently, giving the corresponding tetrasubstituted alkenylborane **4na** (Table 4, entry 3). The reactions of aryl-9-BBN derivatives with electron-donating (**2o**: *p*-MeO) or -withdrawing (**2p**: *p*-F) substituents afforded the corresponding products (entries 4 and 5).

Table 4. Scope of Alkenyl- and Arylboranes[a]



entry	organoborane	product	yield (%)[b]
1	2l	4la	34 (75)[c]
2	2m	4ma	64
3	2n	4na	93
4	2o	4oa	64
5	2p	4pa	91

[a]Conditions of carboboration reaction: **3a**, 0.3 mmol; **2**, 0.3 mmol; PBu_3, 10 mol % (entries 1−3 and 5) or 20 mol % (entry 4); THF, 80 °C, 8 h. [b]Yield of the isolated product (silica gel chromatography). ^{1}H NMR yield is in parentheses. [c]The isolated yield was significantly reduced as compared with the ^{1}H NMR yield because of the material loss during silica gel chromatography.

Phosphine catalysis triggered by conjugate addition of the P center of the phosphine to the alkynoate is known in the literature.[9] On the basis of this knowledge, we propose a catalytic mechanism as shown in Figure 2, which involves the conjugate

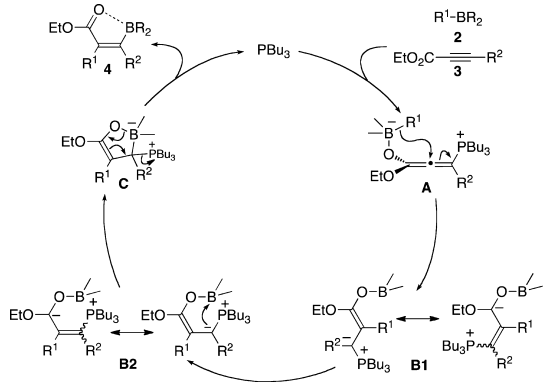


Figure 2. A possible catalytic cycle.

addition of PBu_3 to the alkynoate **3** with the assistance of Lewis acidic activation of the carbonyl group with the organoborane **2** to form a zwitterionic allenolate intermediate (**A**). The *B*-substituent (R^1) in **A** migrates to the *sp*-hybridized central carbon of the allene moiety to form a phosphonium ylide (**B1**).[11] After conversion of **B1** to its geometrical isomer **B2**, the ylide carbon forms a bond with the proximal boron atom to afford cyclic borate **C**. Finally, elimination of Bu_3P associated with B−O bond cleavage affords the alkenylborane **4**. The B−O interaction in **C**

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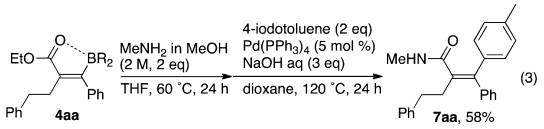
and the concerted nature of the final elimination step is responsible for the *anti* stereochemistry of the carboboration.

The trisubstituted alkenylborane obtained by the phosphine-catalyzed carboboration was used to demonstrate the synthetic utility (eq 3). Although attempts at direct Suzuki–Miyaura



(3)

coupling with **4aa** were unsuccessful, the conversion of the ester group into a secondary amide gave an organoboron derivative suitable for Pd-catalyzed coupling with 4-iodotoluene to afford tetrasubstituted alkene **7aa**.[12]

In summary, phosphine-catalyzed *anti*-selective carboboration of alkynoates with alkyl-, alkenyl-, or arylboranes to form β-boryl acrylates was reported. Interestingly, the carboboration across the polar C–C triple bond occurred with inverse electronic demand with regard to the regioselectivity, with the less electronegative B atom being delivered to the positively charged β carbon atom. The regioselectivity and *anti* stereoselectivity were both complete and robust. In addition, a broad substrate scope with excellent functional group compatibility was confirmed. Accordingly, this phosphine-catalyzed protocol provides a new and efficient strategy for organic synthesis mediated by organoboron compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data for all new compounds (PDF). 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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(2) For a review on the synthesis of multisubstituted alkenes, see: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698.

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