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Copper(I)-Catalysed Stereoselective Debromoborylation of Aliphatic 1,1-Dibromo-1-Alkenes with Bis(pinacolato)diboron

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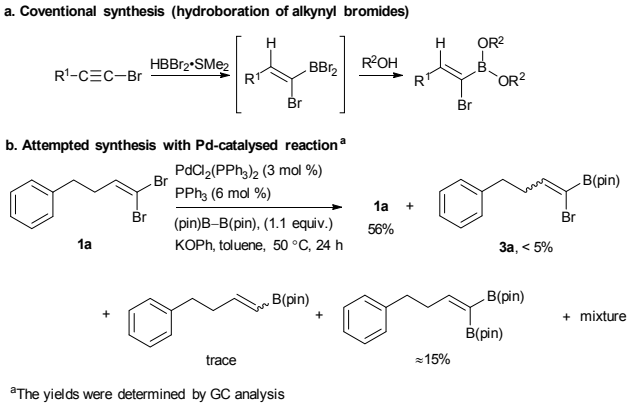
Yadong Pang, Ryoto Kojima and Hajime Ito*

A stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes to prepare (*Z*)-1-bromo-1-alkenylboronate esters using copper(I) catalysts was developed. The debromoborylation of various aliphatic 1,1-dibromo-1-alkenes in the presence of a copper(I) catalyst and bis(pinacolato)diboron proceded smoothly to produce (*Z*)-1-bromo-1-alkenylboronate esters in good yields with only *Z* geometry.

Organoboronic acids and their derivatives, especially alkenylboronate esters, are powerful and versatile reagents in organic synthesis because of their high stability, low toxicity, and synthetic utility in many reactions such as the Suzuki–Miyaura cross-coupling reaction.[1] In addition, (*Z*)-1-bromo-1-alkenylboronate esters are useful organoboron synthetic intermediates in organic synthesis. They are known to undergo cross-coupling reactions with organozinc reagents[2] and intramolecular nucleophilic substitution reactions with nucleophiles such as hydrides,[3] Grignard reagents,[4] organolithium reagents,[4] allylmagnesium bromide,[5] trimethylsilylmethyllithium[6] and trimethylgermyllithium.[7] However, only one method to synthesise (*Z*)-1-bromo-1-alkenylboronate esters has been developed: hydroboration of alkynyl bromides (Scheme 1a).[2-7] The synthesis of alkynyl halides requires harsh reaction conditions and has poor functional group compatibility. Therefore, the development of a simple, mild and efficient method for the direct preparation of (*Z*)-1-bromo-1-alkenylboronate esters remains highly desirable. Our research focuses on the stereoselective debromoborylation of 1,1-dibromo-1-alkenes, which are readily available from the corresponding carbonyl compounds through the Wittig reaction.[8]



Scheme 1 Synthesis of (*Z*)-1-bromo-1-alkenylboronate esters.

To develop a more convenient reaction pathway to alkenylboronate esters, we first considered the Pd-catalysed borylation with bis(pinacolato)diboron, which was developed by Miyaura and Ishiyama and is a standard procedure for transformation of alkenyl bromide. However, similar to the results already reported by Cao's group,[10] the Pd-catalysed borylation of 1,1-dibromo-1-alkene **1a** failed. Only a small amount of the desired product was obtained along with a monoborylated alkene and a diboryl alkene in a complex mixture. (Scheme 1b).[9]

Very recently, several groups reported copper(I)-catalysed reactions of 1,1-difluoro-1-alkenes. Three different groups (led by Cao, Ogoshi and Niwa, and Wang) independently reported monodefluoroborylation reactions of aryl 1,1-difluoro-1-alkenes with bis(pinacolato)diboron in the presence of a copper(I) catalyst to afford (*Z*)-1-fluoro-1-alkenylboronate esters (Scheme 2a).[10-12] This reaction proceeds through the addition of a borylcopper(I) intermediate to the 1,1-difluoro-1-alkene and subsequent β-elimination to give the corresponding defluoroborylation products. At the almost same time, we and Shi's group also reported selective hydrodefluorinations of aryl 1,1-difluoro-1-alkenes with a

Division of Applied Chemistry and Frontier Chemistry Center,
Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.
E-mail: hajito@eng.hokudai.ac.jp

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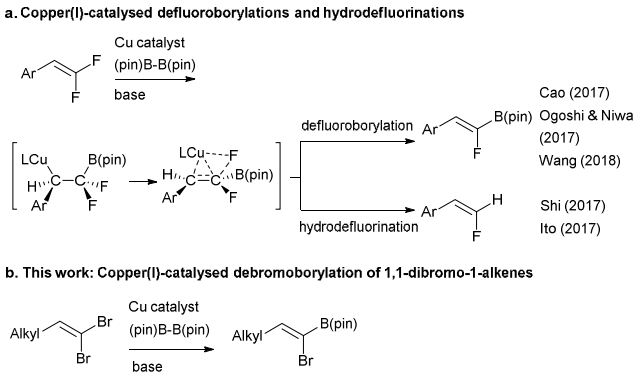
copper(I) catalyst to produce monofluoroalkenes, in which the same key intermediate would be present (Scheme 2a).[13,14]

Inspired by these results and the similar reactivity of F and Br, we envisioned that the selective debromoborylation of 1,1-dibromo-1-alkenes should be possible. Herein, we report a novel and efficient method for the synthesis of (*Z*)-1-bromo-1-alkenylboronate esters via copper(I)-catalysed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron in the presence of a copper(I) catalyst (Scheme 2b).

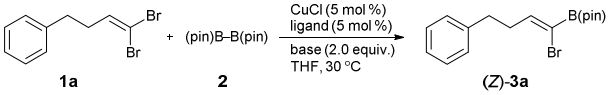


Scheme 2 Copper(I)-catalysed reactions of 1,1-dihalo-1-alkenes.

Our research commenced with the screening of reaction conditions for the borylation of (4,4-dibromobut-3-en-1-yl)benzene **1a** with bis(pinacolato)diboron as the model reaction (Table 1). Initially, a trace amount of the desired product was observed in the absence of a ligand (entry 1). Then, we found that Xantphos was a preferred ligand among common ligands such as PPh_3, dppp, dppbz, IPr·HCl, and 1,10-phen (entries 2–7). Further screening of a series of different bases revealed that only NaOMe (2.0 equiv.) could afford the desired product (*Z*)-**3a** in good yield (entries 8–13). In particular, the use of a relatively strong base, sodium *tert*-butoxide, could afford the corresponding bromoalkyne as a major by-product and no desired product was obtained (entry 10). To our delight, this debromoborylation reaction occurred with high (*Z*)-selectivity and no (*E*)-isomer was detected by GC and NMR analyses. The structure of the favourable stereoisomer was confirmed by single-crystal X-ray diffraction analysis of (*Z*)-**3n** (see ESI).

With the optimal reaction conditions in hand (Table 1, entry 7), a series of aliphatic 1,1-dibromo-1-alkene substrates that were prepared from aliphatic aldehydes was examined to investigate the scope of the debromoborylation reaction (Table 2). The debromoborylation reaction proceeded efficiently to give the corresponding (*Z*)-brominated alkenyl boronate esters **3** in moderate to good yields and no (*E*)-isomer was observed in each case. However, we found that purification of the boronate esters (*Z*)-**3** without loss was difficult using typical chromatographic techniques because they were easily hydrolysed in silica gel; thus, the isolated yields were lower than the corresponding NMR yields. Substrates with aryl groups (**1a–e**) or a heteroaryl moiety **1f** did not hamper this debromoborylation process and afforded the corresponding products [(*Z*)-**3a–f**] in high NMR and moderate isolated yields, [(*Z*)-**3a**, 85% (55%); (*Z*)-**3b**, 77% (52%); (*Z*)-**3c**, 83% (58%); (*Z*)-**3d**, 81% (62%); (*Z*)-**3e**, 71% (55%); (*Z*)-**3f**, 87% (62%)]. The reactions of substrates with simple alkyl chains (**1g–j**) gave the desired products in high NMR yields and moderate isolated yields [(*Z*)-**3g**, 92% (59%); (*Z*)-**3h**, 83% (62%); (*Z*)-**3i**, 90% (57%); (*Z*)-**3j**, 85% (58%)]. Substrates with chlorine (**1k**), alkene (**1l**), carbamate (**1m**) and imide (**1n**) functional groups were also tolerated [(*Z*)-**3k**, 77% (57%); (*Z*)-**3l**, 90% (54%); (*Z*)-**3m**, 75% (51%); (*Z*)-**3n**, 66% (50%)]. Unfortunately, when (2,2-dibromovinyl)cyclohexane **1o**, which bears a tertiary carbon at the α-position of the double bond of the 1,1-dibromo-1-alkene, was used as a substrate under the optimal reaction conditions, no reaction occurred and the desired product (*Z*)-**3o** was not obtained, probably because of steric hindrance. Furthermore, when (2,2-dibromovinyl)benzene **1p** was used as a substrate, the starting material was recovered mostly and the desired product (*Z*)-**3p** was also not obtained even under the optimised conditions.

Table 1 Screening of reaction conditions for the debromoborylation of aliphatic 1,1-dibromo-1-alkenes[a]



1a **2** (*Z*)-**3a**

entry	ligand	base	yield (%)[b]
1	-	NaOMe	4
2	PPh_3[c]	NaOMe	7
3	dppp	NaOMe	61
4	dppbz	NaOMe	58
5	IPr·HCl	NaOMe	13
6	1,10-phen	NaOMe	18
7	Xantphos	NaOMe	85
8	Xantphos	NaOMe[d]	58
9	Xantphos	KOMe	51
10	Xantphos	Na(O-*t*-Bu)	trace[e]
11	Xantphos	KOAc	trace
12	Xantphos	K_2CO_3	trace
13	Xantphos	LiOMe	trace

[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.3 mmol), solvent (1 mL), 3 h; [b]Yields were determined by ^{1}H NMR analysis; [c]10 mol % was used; [d]1.5 equiv. was used. [e] 1-Bromo-4-phenyl-but-4-yne was detected in approx. 40% yield by ^{1}H NMR analysis.

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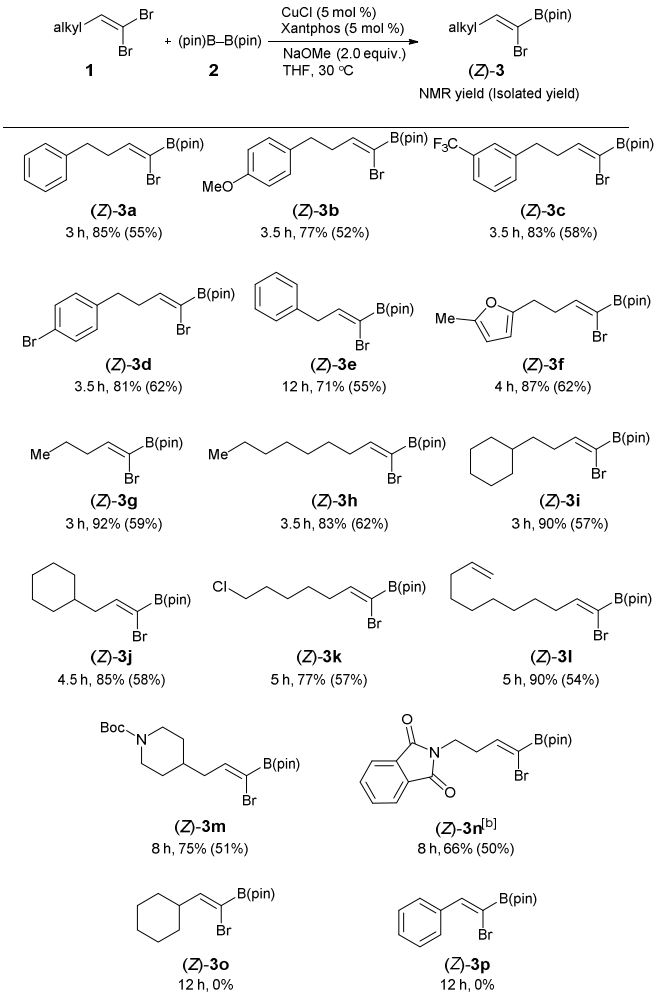
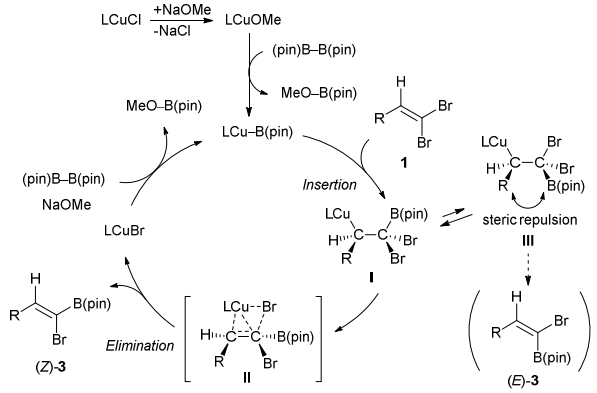
Table 2 Scope of the debromoborylation of aliphatic 1,1-dibromo-1-alkenes[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.3 mmol), solvent (1 mL). Yields were determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses. [b]CuCl (10 mol %), Xantphos (10 mol %), and solvent (1.5 mL) were used

Based on the above observations and previous reports,[10-15] a mechanism for the copper(I)-catalysed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron is proposed (Scheme 2). Initially, transmetallation of the phosphine-ligated copper(I) catalyst LCuOMe, which is generated in situ from LCuCl and NaOMe, with bis(pinacolato)diboron provides the nucleophilic phosphine-coordinated borylcopper(I) complex LCu–B(pin). Subsequent insertion of the carbon-carbon double bond of the 1,1-dibromo-1-alkene **1** into the Cu–B bond of the borylcopper(I) complex would lead to the generation of β-borylalkylcopper(I) species **I** with the perfect regioselectivity since forming the C–B bond should be occurred at the more electron-positive olefinic carbon. β-Elimination of the borylalkylcopper(I) intermediate **II** affords the desired product (*Z*)-**3**, along with generation of LCuBr. The other conformational isomer of the intermediate **III**, which can afford (*E*)-**3**, should be less energetically favourable than **II** because of the steric repulsion between the alkyl group and bulky B(pin). This can explain the exclusive formation of the (*Z*)-isomer of **3**. Finally, LCuBr further reacts with bis(pinacolato)diboron and NaOMe to regenerate the active species LCu–B(pin) and complete the catalytic cycle.



Scheme 3 Plausible mechanism for the copper(I)-catalysed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron.

In conclusion, we have developed a new and efficient method to synthesise (*Z*)-1-bromo-1-alkenylboronate esters via copper(I)-catalysed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron in the presence of NaOMe and Xantphos at 30 °C. The borylation reaction exhibits a wide substrate scope, good functional group compatibility and affords a variety of (*Z*)-brominated borylation products in moderate to good yields. At the same time, our study is the first example of the selective debromoborylation of 1,1-dibromo-1-alkenes, which is expected to become a powerful synthetic approach to construct a broad range of intermediates and materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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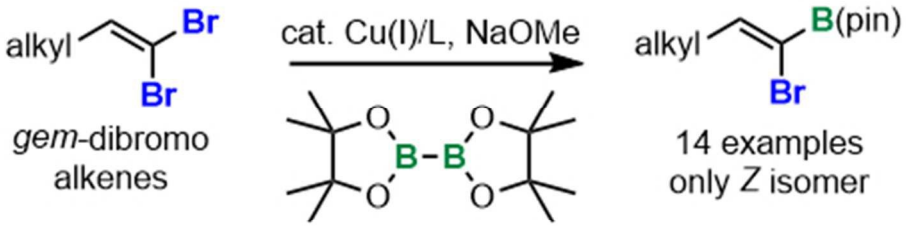

the first example of the selective debromoborylation of *gem*-dibromoalkenes