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# A novel route to stereodefined cyclopropyl-substituted alkenes

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**Abstract**

The first $Tl_2CO_3$ or $Ag_2O$ assisted Suzuki-type cross-coupling of stereodefined cyclopropylboronic acids with haloalkenes without electron-drawing groups to give the corresponding stereodefined cyclopropyl-substituted alkenes in good yields is described. The configurations of both cyclopropyl and alkenyl functions were retained in the reaction. 

*Keywords:* cyclopropylboronic acid; cyclopropyl-substituted alkenes; cross-coupling; palladium.

The stereo- and regiospecific synthesis of cyclopropyl-substituted alkenes is of importance in organic chemistry.[1] During the past 15–20 years, methods for the preparation of cyclopropyl-substituted alkenes have been developed utilizing organometallic compounds. For example, Piers et al. reported a new route to cyclopropyl-substituted alkenes by the palladium-catalyzed coupling of vinyl halides with stereodefined cyclopropylzinc reagents.[2a] However, the preparation of cyclopropylzinc is troublesome. Charette and Giroux[3] recently reported a new method for the synthesis of stereodefined cyclopropyl-substituted alkenes by a Suzuki-type coupling of alkenylboronic esters with substituted iodocyclopropanes. However, the preparation of iodocyclopropanes was also difficult because toxic organotin reagents were involved and the yield of the iodocyclopropanes was low (30%).[4]

Stereodefined cyclopropylboronic acids have been readily obtained by cyclopropanation of alkenylboronic acids which are stable to air and moisture, making them easy to handle. Consequently, we attempted to prepare cyclopropyl-substituted alkenes via Suzuki-type coupling of cyclopropylboronic acids with alkenyl halides. Using toluene as a solvent and in the presence of $K_3PO_4 \cdot 3H_2O$ and a catalytic amount of $Pd(PPh_3)_4$, the cross-coupling of cyclopropylboronic acid with bromoacrylates readily occurred to give the desired cyclopropyl-substituted acrylates in good yield.[5] However, under the above conditions the alkenyl bromides without electron-drawing groups did not couple with cyclopropylboronic acids. To generalize the coupling reaction of cyclopropylboronic acids with other alkenyl halides, we reinvestigated the conditions by using *trans*-butylcyclopropylboronic acid and (*Z*)-β-bromostyrene and herein we wish to report recent results.

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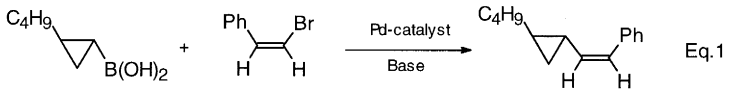
Base is essential for the Suzuki-type cross-coupling.[6] In the cross-coupling of alkenylboronates and arylboronates with electrophiles in the presence of palladium catalyst, bases, such as alkali metal hydroxide, alkoxide, carbonate, phosphate etc., can be used. However, the use of all of the above-mentioned bases did not lead to the coupling of cyclopropylboronic acids with alkenyl halides (Table 1, entries 1–4). It was reported that thallium(I) salts could benefit the catalytic cross-coupling of arylboronic or alkenylboronic acids (esters) with some electrophiles.[7] Suzuki et al. also reported that thallium(I) salts effectively promote the coupling reaction of alkylboronic esters with alkenyl or aryl halides.[8] As expected, by using $Tl_2CO_3$ as the base and THF as the solvent, a 55% yield of the coupling product was obtained (entry 5). Using $Ag_2O$[9] instead of $Tl_2CO_3$ as a base the reaction also affords the coupling product in 55% yield (entry 12). Dioxane appeared to be a better solvent than THF, DMF or toluene (entry 7 versus 5 and 6, and entry 13 versus 12) and the addition of aqueous hydroxide, especially potassium hydroxide, not only to the $Tl_2CO_3$ system but also to the $Ag_2O$ system made the coupling yield increase (entry 10 versus 7, and entries 14 and 15 versus 13). The coupling reactions of the cyclopropylboronic acids with alkenyl halides were conducted under optimum conditions (Table 1, entries 15 and 11). The experimental results are shown in Table 2.

Table 1
Reaction conditions of the coupling of *trans*-2-butylcyclopropylboronic acid with (*Z*)-β-bromostyrene



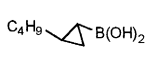
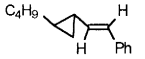
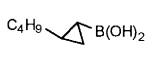
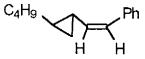
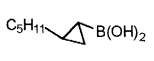
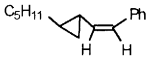
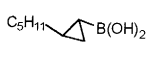
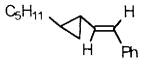
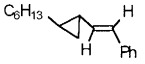
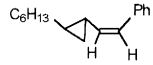
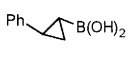
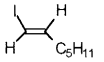
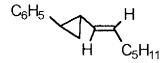
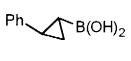
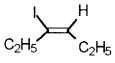
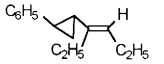
Eq.1

| entry[a] | conditions | yield[b] |
|---|---|---|
| 1 | NaOH, THF, reflux, 15 h | n.r. |
| 2 | $Na_2CO_3$, THF, reflux, 12 h | n.r. |
| 3 | $K_3PO_4.3H_2O$, toluene, 100°C, 24 h | n.r. |
| 4 | NaOMe, benzene, reflux, 15 h | n.r. |
| 5 | $Tl_2CO_3$, THF, reflux, 15 h | 55% |
| 6 | $Tl_2CO_3$, toluene, 80°C, 12 h | 47% |
| 7 | $Tl_2CO_3$, dioxane, 80°C, 12 h | 64% |
| 8 | $Tl_2CO_3$, DMF:$H_2O$ (1:1), 80°C, 10 h | 45% |
| 9 | $Tl_2CO_3$, dioxane:$H_2O$ (1:1), 80°C, 10 h | 74% |
| 10 | $Tl_2CO_3$, dioxane, NaOH (3 eq), 80°C, 8 h | 75% |
| 11 | $Tl_2CO_3$, $Ag_2O$, NaOH (3 eq), dioxane, 80°C, 5 h | 78% |
| 12 | $Ag_2O$, THF, reflux, 15 h | 55% |
| 13 | $Ag_2O$, dioxane, 80°C, 11 h | 62% |
| 14 | $Ag_2O$, NaOH (3 eq), dioxane, 80°C, 10 h | 76% |
| 15 | $Ag_2O$, KOH (3 eq), dioxane, 80°C, 8 h | 82% |

[a] All the reactions were carried out using a mixture of 2-butylcyclopropylboronic acid (1.1 mmol), (*Z*)-β-bromostyrene (1.0 mmol), $Pd(PPh_3)_4$ (3% mmol), base (1.5 mmol) under nitrogen atmosphere. [b] Isolated yields.

Table 2 demonstrates that the cross-coupling between various cyclopropylboronic acids and alkenyl halides without electron-drawing functionality readily occurs to afford the expected products in good yields. The $^1H$ NMR and 2D $^1H$–$^1H$ NOESY spectra confirmed that the configurations of both the cyclopropyl and alkenyl functions were the same as the starting materials. For example, one of the alkenyl protons ($\delta$ 5.77, $H^e$) of compound **3e**[10] showed a very strong NOE interaction with three of the cyclopropyl protons ($\delta$ 0.85–0.88, $H^b$; 0.57–0.61, $H^d$; 1.29–1.52, $H^a$) and no NOE interaction with the fourth ($\delta$ 0.61–0.66, $H^c$). Furthermore, the proton $H^a$ also showed an NOE interaction with $H^c$. The *J* value (15.73 Hz) between $H^e$ and $H^f$ showed that the configuration of the alkene in **3e** was *trans* of that of

Table 2
Coupling reactions of cyclopropylboronic acids with alkenyl halides

| entry | cyclopropylboronic acids | alkenyl halides | products | | procedure[a] | yield[b] |
|---|---|---|---|---|---|---|
| 1 |  |  |  | **3a** | A<br>B | 73%<br>80% |
| 2 |  |  |  | **3b** | A<br>B | 79%<br>82% |
| 3 |  |  |  | **3c** | A | 77% |
| 4 |  |  |  | **3d** | A | 76% |
| 5 |  |  |  | **3e** | A<br>B | 82%<br>83% |
| 6 |  |  |  | **3f** | A<br>B | 71%<br>76% |
| 7 |  |  |  | **3j** | B | 78% |
| 8 |  |  |  | **3h** | B | 75% |

[a] All the reactions were carried out at 80℃ in 4 ml dioxane using a mixture of the cyclopropylboronic acids (1.1 mmol), bromoalkenes(1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol). Procedure A: $Tl_2CO_3$ (1.5 mmol) and NaOH (3N, 3.3 eq) as the base. Procedure B: $Ag_2O$ (1.5 mmol) and KOH(3N, 3.3 eq) as the base under nitrogen atmosphere. [b] Yields of isolated products purified by flash chromatography(100% hexane).

the starting bromoalkene. All these facts suggest the configurations of both the cyclopropyl and alkenyl functions were retained in the reactions. Therefore, the reaction is a novel method for the synthesis of stereodefined cyclopropyl-substituted alkenes.

In conclusion, we have reported the first cross-coupling of cyclopropylboronic acids with haloalkenes without electron-drawing groups under very mild conditions. Stereodefined cyclopropylboronic acids and haloalkenes are easily available, thus our method has opened the door to stereocontrollable construction of cyclopropyl-substituted alkenes from stereodefined cyclopropylboronic acids and haloalkenes.

## Acknowledgements

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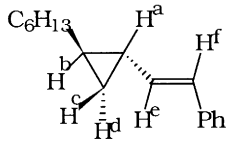
10. Physical constants of 1-[*E*-(2-phenyl-1-vinyl)]-2-hexylcyclopropane(**3e**):




Colorless oil; anal. calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59; found: C, 89.36; H, 10.76. $^1$H NMR (300 MHz, $CD_3Cl$) $\delta$ ppm: 7.27 (5H, m, -Ar), 6.39 (1H, d, $J_1$=15.73 Hz, $H^f$), 5.77 (1H, dd, $J_1$=15.73, $J_2$=8.91 Hz, $H^e$), 1.29–1.52 (11 H, br, -$(CH_2)_5$-+$H^a$), 0.85–0.88 (4H, m, $CH_3$+$H^b$), 0.57–0.61(1H, m, $H^d$), 0.61–0.66 (1H, m, $H^c$); $^{13}$C NMR (300 MHz, $CD_3Cl$) $\delta$ ppm: 137.967, 134.821, 128.518, 126.828, 126.474, 125.576, 33.976, 31.973, 29.415, 22.758, 22.443, 21.749, 14.576, 14.129; MS (EI): 228 ($M^+$, 68.16), 129 (100), 143 (48.67), 128 (33.57), 130 (31.58), 115 (28.87), 91 (24.81), 144 (14.42). IR $cm^{-1}$: 2925 (s), 1650 (m), 1600 (m), 1493 (m), 956 (m), 744 (m), 692 (s).