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Palladium-catalyzed cross-coupling of cyclopropylboronic acids with alkenyl triflates

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Abstract

A novel method for the synthesis of stereodefined cyclopropyl-substituted alkenes, based on the Suzuki-type cross-coupling reaction between cyclopropylboronic acids and various alkenyl triflates, is described. It was found that the environment of the alkenyl triflate plays an important role in the reaction, and that the use of an appropriate base can make the reaction proceed readily to give stereodefined cyclopropyl-substituted alkenes in good to high yield.

Keywords: cross-coupling reaction; cyclopropylboronic acids; alkenyl triflates.

Stereodefined cyclopropyl-substituted alkenes are present in many natural products, such as ambruticin, constanolactone E–G and dictyopterene B.[1] Cyclopropyl-substituted alkene derivatives can also undergo many versatile transformations.[2] Moreover, in recent years the stereodefined cyclopropyl unit is increasingly being incorporated into biologically active molecules. For example, the synthesis of cyclopropyl analogues of histamine H_3 receptor antagonist[3] and Tamoxifen[4] were reported recently. Although several routes have been available for the synthesis of cyclopropyl-substituted alkenes,[5] the utility of these methods suffers from certain drawbacks, such as poor stereoselectivity,[3a] restricted generality[3b] and the need for toxic chemicals.[3c]

With our ongoing interest in the palladium-catalyzed cross-coupling reactions of cyclopropylboronic acids,[6] and considering that alkenyl triflates can be easily obtained from carbonyl compounds,[7] we recently investigated the Suzuki-type cross-coupling reaction of cyclopropylboronic acids with alkenyl triflates as a convenient method of introducing cyclopropyl groups.

Initially, we examined the cross-coupling of alkenyl triflate (**2a**), which was generated by the triflation of ethyl 1-oxo-2-cyclopentylcarboxylate, with *trans*-2-pentylcyclopropylboronic acid (**1**) under the optimum reaction conditions for the coupling of bromoacrylate[6b] (defined as

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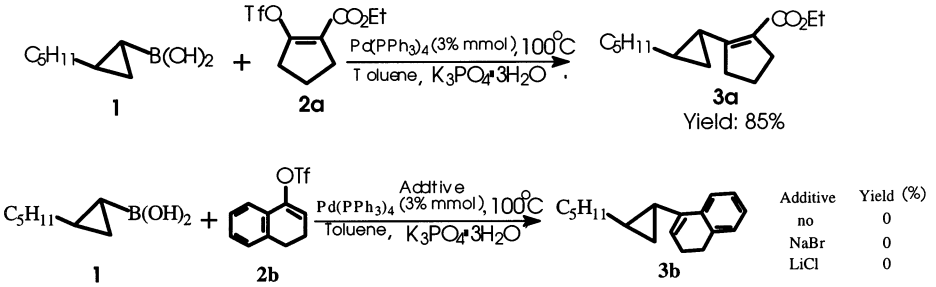
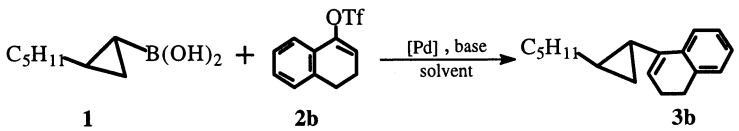
conditions A), and were able to isolate the desired product in 85% yield (Scheme 1). However, the existence of an electron-withdrawing group (–CO_2Et) in the alkenyl triflate is critical to the reaction. Substrates lacking electron-withdrawing groups (**2b**) fail to react with the cyclopropylboronic acid (**1**) under conditions A, even in the presence of metal halides (LiCl, NaBr Scheme 1).



Scheme 1.

In this case, we reinvestigated the coupling reaction conditions of alkenyl triflates with cyclopropylboronic acid. The results are shown in Table 1.

Table 1
Effects of solvent and base on the coupling of *trans*-pentylcyclopropylboronic acid **1** with alkenyl triflate **2b**[a]



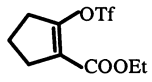
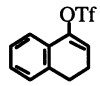
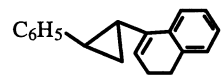
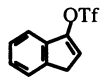
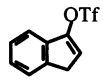
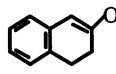
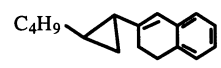
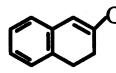
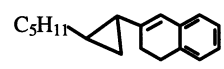
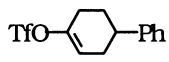
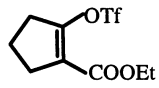
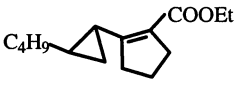
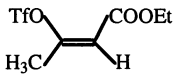
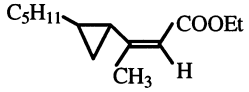
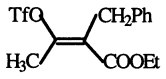
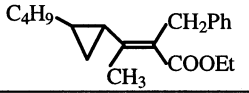
Entry	Conditions	Yield (%)[b]
1	THF, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$, 70°C	0
2	THF, $K_3PO_4{\cdot}3H_2O$, $Pd(dppf)Cl_2$, 70°C	0
3	Dioxane, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$, 70°C	0
4	DMF, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$, 120°C	0
5	Dioxane, Ag_2O:KOH(1:2), $Pd(PPh_3)_4$, 100°C	Trace
6	Dioxane, Cs_2CO_3:KF·$2H_2O$(1:2), $Pd(PPh_3)_4$, 100°C	23[c]
7	Toluene, Cs_2CO_3:KF·$2H_2O$(1:2), $Pd(PPh_3)_4$, 100°C	43
8	Toluene, Cs_2CO_3:KF·$2H_2O$(1:2), $Pd(PPh_3)_4$, 80°C	69
9	Toluene, Cs_2CO_3:KF·$2H_2O$(1:3), $Pd(PPh_3)_4$, 80°C	74
10	Toluene, Cs_2CO_3:KF·$2H_2O$(1:4), $Pd(PPh_3)_4$, 80°C	67
11	Toluene, Cs_2CO_3, $Pd(PPh_3)_4$, 80°C	49[c]
12	Toluene, KF·$2H_2O$, $Pd(PPh_3)_4$, 80°C	0

[a] Reactions were carried out using 3% mmol of catalyst, base (in total 3.2 equiv.), NaBr 1 equiv., *trans*-2-pentylcyclopropylboronic acid (1.1 mmol), alkenyl triflate (1 mmol) in 4 ml solvent for 16 hours.
[b] Isolated yield based on triflate.
[c] The alkenyl triflate was not consumed completely.

In the cross-coupling reaction of alkenyl triflates with aryl- and alkenyl-boronic acids, Suzuki and co-workers[8] found that the reaction was more efficient in an ethereal solvent. However, under these conditions, the coupling reaction of alkenyl triflates without electron-withdrawing groups (**2b**) with cyclopropylboronic acid did not take place (entries 1–3). In the total synthesis

of palytoxin, Kishi and co-workers[9] reported that the use of Ag_2O and/or KOH benefited the coupling reaction of alkenylboronic acids with alkenyl halides, and under these reaction

Table 2
Cross-coupling reaction of cyclopropylboronic acids with alkenyl triflates[a]

Entry	Cyclopropylboronic acids (1)	Alkenyl triflate(2)	Product[b] (3)		Yield[c] (%)
1				**3a**	73(85)
2				**3b**	74(0)
3				**3c**	67(0)
4				**3d**	73(0)
5				**3e**	79(0)
6				**3f**	71(0)
7				**3g**	67(0)
8				**3h**	63(0)
9				**3i**	75(86)
10				**3j**	67(73)
11				**3k**	69(78)

a . cyclopropylboronic acid (1.1 mmol), alkenyl triflate(1.0 mmol), 3% mmol of $Pd(PPh_3)_4$, in toluene (4 ml). **Conditions A**: 3.3 equiv. $K_3PO_4 \cdot 3H_2O$ was used as the base at 100°C; **Conditions B**: 0.8 equiv. Cs_2CO_3 and 2.4 equiv. $KF \cdot 2H_2O$ were used as the base and 1 equiv. NaBr was added at 80°C. b. All the products gave satisfactory elemental analysis; ^1H NMR; MS and IR spectra. c. Isolated yields based on alkenyl triflates under **conditions B** (the data in parenthesis are the yields under **conditions A**).

conditions the cross-coupling reaction of cyclopropylboronic acids with alkenyl bromides did work readily.[6d] Unfortunately, the use of Ag_2O and KOH did not cause the alkenyl triflate to react with cyclopropylboronic acids (entry 5). When the reaction was carried out in the presence of a catalytic amount of $Pd(PPh_3)_4$ and $Cs_2CO_3/KF{\cdot}2H_2O$ (mole ration 1:2), using dioxane as the solvent, the anticipated reaction occurred. However the reaction did not proceed to completion, and the desired product was obtained in only 23% yield (entry 6). Conducting the reaction in the nonpolar solvent toluene, a 43% yield of the desired coupling product was obtained (entry 7). Considering the sensitivity of the desired cyclopropyl-substituted alkene products to high temperature (e.g. to a [3+2] ring enlargement reaction[10]), we lowered the reaction temperature to 80°C causing an improvement in the yield (entry 8). A series of experiments revealed that when the reaction was carried out using a combination of Cs_2CO_3 and $KF{\cdot}2H_2O$ as the base (mole ratio 1:3, defined as conditions B), the yield of the desired product was slightly improved (entry 9). Using the base Cs_2CO_3 or $KF{\cdot}2H_2O$ alone, the reaction did not proceed to completion or take place (entries 11, 12).

A variety of alkenyl triflates and cyclopropylboronic acids were used to evaluate the scope of the above-mentioned coupling reaction conditions A and B. The experimental results are shown in Table 2.

As shown in Table 2, various alkenyl triflates can couple smoothly with cyclopropylboronic acids to give the corresponding cross-coupling products in moderate to good yields under conditions B. For alkenyl triflates without electron-withdrawing groups (e.g. $-CO_2Et$), the use of the bases Cs_2CO_3 and $KF{\cdot}2H_2O$ was essential. For alkenyl triflates bearing electron-withdrawing group ($-CO_2Et$), reaction conditions A can offer somewhat higher yields. The ^1H NMR spectra of the products and 2D ^1H NMR of part of products[11] clearly showed that the configurations of both cyclopropyl groups and double bonds were retained during the cross-coupling reactions.

In summary, we have demonstrated the cross-coupling of cyclopropylboronic acids with various alkenyl triflates. Because of the ready availability of alkenyl triflates from their ketone precursors, the success of this reaction provides a novel route to stereodefined cyclopropyl-substituted alkenes by the introduction of a stereodefined cyclopropyl group.

Acknowledgements

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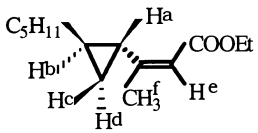

11. The 2D ^{1}H NMR (400 MHz) spectrum of product **3j**: δ_H($CDCl_3$, TMS): 5.68 (s, 1H, H^e); 4.11–4.19 (q, 2H, J=7.11, $O\underline{CH_2}CH_3$); 2.95–3.02 (ddd, J=5.8Hz, J=5.7 Hz, J=8.9 Hz, 1H, H^a); 1.53 (s, 3H, CH_3^f); 1.25–1.37 (m, 11H, $4\times\overline{CH_2}+O\overline{CH_2CH_3}$); 1.16–1.25 (ddd, J=5.8 Hz, J=9.0 Hz, J=4.8 Hz, 1H, H^b); 0.86–0.95 (m, 4H, CH_3+H^d); 0.64–0.68 (ddd, J=5.7 Hz, J=9.0 Hz, J=4.8 Hz, 1H, H^c). The proton H^d showed strong NOE interaction with H^b; H^c and H^f of CH_3, but no NOE interaction with H^a. H^a showed strong NOE interaction with H^b and CH_2 of C_5H_{11}. The proton H^e showed strong NOE interaction with H^f of CH_3, but no NOE interaction with H^a. All these facts suggest that the configurations of both the cyclopropyl and alkenyl groups in the coupled product were the same as those in starting materials.