Cross-coupling reaction of cyclopropylboronic acid with bromoarenes

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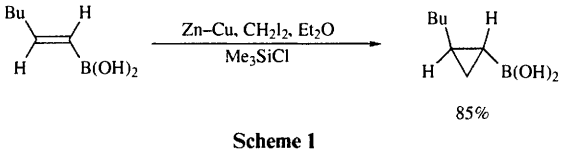
The cross-coupling reaction of *trans*-2-butylcyclopropylboronic acid with bromoarenes proceeds readily in the presence of $Pd(PPh_3)_4$ and $K_3PO_4 \cdot 3H_2O$ to give stereodefined *trans*-2-butylcyclopropylarenes in high yields.

The cross-coupling reaction[1] of organometallic reagents with electrophiles in the presence of transition metals is a powerful method for forming carbon–carbon bonds. Suzuki[2] reported a number of cross-coupling reactions of aryl-, alkenyl- and alkylboron compounds with electrophiles and showed that the cross-coupling reactions of organoboron compounds had many advantages. However, the yield of cross-coupling products for the *sec*-alkylboron compounds was low.[3] In addition, it was not described whether the configuration of the alkyl group on the boron atom was retained in the coupling process, although the configuration of the alkenylboron compound was retained during the reaction.[3]

Stereodefined alkenylboronic acids (or esters) are readily available,[4] and alkenylboronic acid esters have been reported to react readily with diethylzinc and diiodomethane or with diazomethane in the presence of palladium acetate, to give stereospecific cyclopropylboronic acid esters.[5] Recently, we successfully accomplished the cyclopropanation of *E*-alkenylboronic acids using the Simmons–Smith reaction,[6] in which the Zn–Cu couple was activated by a catalytic amount of chlorotrimethylsilane, and obtained stereodefined *trans*-2-alkylcyclopropylboronic acids in good yields (Scheme 1).

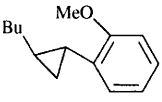
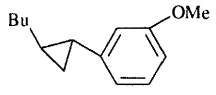
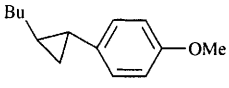
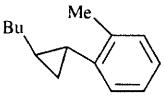
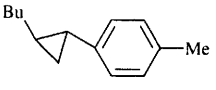
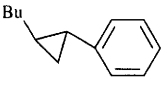
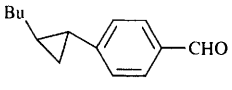
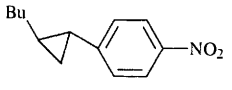
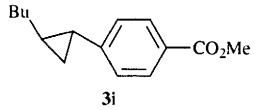


Scheme 1

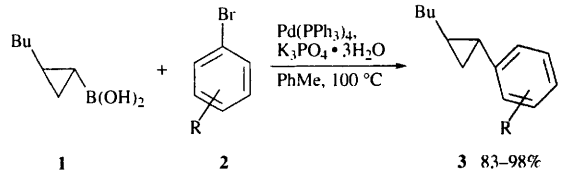
To the best of our knowledge, although many cyclopropyl metallic derivatives (such as Al, Si, Hg, Ga *etc.*) have been prepared,[7] no report of the cross-coupling reaction of cyclopropylmetallic compounds with organic halides in the presence of a transition metal has appeared in the literature. Here we report the results of the cross-coupling reaction of *trans*-2-butylcyclopropylboronic acid with bromoarenes in the presence of Pd^0 and base. The reaction conditions were optimized and it was found that *trans*-2-butylcyclopropylboronic acid **1** reacted readily with bromoarenes **2** in the presence of 3 mol% $Pd(PPh_3)_4$ and $K_3PO_4 \cdot 3H_2O$ in toluene at 100 °C to give pure products **3** in high yields (Scheme 2). The results are shown in Table 1. All products were found to be the *trans*-isomer by GC and ^1H NMR spectroscopy. For example, two of the aryl protons (δ 7.07, H^e, H^f) of compound **3i** showed very strong NOE interactions with three of the cyclopropyl protons (δ 1.61–1.68, H^a; 1.05–1.12, H^b; 0.92–0.98, H^c), but no NOE interaction with a fourth (δ 0.81–0.88, H^d). Furthermore, the proven H^a also showed an NOE interaction with H^d in the cyclopropyl skeleton. All this suggested **3i** was pure *trans*-2-butylcyclopropylarene and that the configuration of cyclopropylboronic acid was retained during the cross-coupling reaction.

As can be seen from Table 1, the cross-coupling reaction is mild, and some sensitive groups, such as carbonyl, nitro and ester groups, are unaffected by the reaction. Since stereodefined

Table 1 The cross-coupling reaction of *trans*-2-butylcyclopropylboronic acid with bromoarenes[a]

Entry	Bromoarenes	Product[b]	Yield (%)[c]
1	2-Bromoanisole	 **3a**	89
2	3-Bromoanisole	 **3b**	91
3	4-Bromoanisole	 **3c**	83
4	2-Bromotoluene	 **3d**	92
5	4-Bromotoluene	 **3e**	98
6	Bromobenzene	 **3f**	92
7	4-Bromobenzaldehyde	 **3g**	96
8	1-Bromo-4-nitrobenzene	 **3h**	85
9	Methyl 4-bromobenzoate	 **3i**	93

[a] *trans*-2-Butylcyclopropylboronic acid (1.1 mmol), bromoarenes (1.0 mmol), 3 mol% $Pd(PPh_3)_4$, 3.3 equiv. $K_3PO_4 \cdot 3H_2O$ (based on boronic acid) and toluene (4 ml) was stirred at 100 °C under a nitrogen atmosphere. [b] All products were identified by ^1H NMR, IR and mass spectral and elemental analysis or HRMS. [c] Isolated yield.

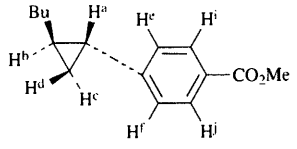


1 2 3 83–98%

R = *o*–OMe, *m*–OMe, *p*–OMe, *o*–Me, *p*–Me, H, *p*–CHO, *p*–NO_2, *p*–CO_2Me

Scheme 2

cyclopropylboronic acids are easily obtained from the cyclopropanation of *E*- or *Z*-alkenylboronic acid, and palladium-catalysed cross-coupling reactions of cyclopropylboronic acid with bromoarenes proceed readily to give pure stereoisomeric cyclopropylarenes in high yields, this reaction might be a general method for preparing stereodefined cyclopropyl substituted arenes. We are continuing to extend the scope of this method and will report further results accordingly.



3i

The preparation of methyl *p*-(*trans*-2-butylcyclopropyl)-benzoate **3i** is representative of the methods used. To a solution of methyl *p*-bromobenzoate (2.15 mg, 1.0 mmol) in toluene (4 ml), *trans*-2-butylcyclopropylboronic acid (156 mg, 1.1 mmol), $K_3PO_4 \cdot 3H_2O$ (879 mg, 3.3 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) were added under a nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 15 h, then cooled to room temperature and water (10 ml) added into the mixture. The mixture was extracted with petroleum (bp 60–90 °C, 2 × 10 ml). The combined organic layer was washed with brine (3 × 10 ml) and dried with $MgSO_4$. After removing the solvent *in vacuo*, methyl *p*-(*trans*-2-butylcyclopropyl)benzoate (216 mg, 93% yield) was isolated by silica gel chromatography, eluting with petroleum–diethyl ether (v:v, 40:1). The product was identified to be pure *trans* isomer† by GC and ^1H NMR spectroscopy.

Acknowledgements

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† $\delta_H(CDCl_3, SiMe_4, 300\ MHz)$ 0.81–0.88 (m, 1 H, H^d), 0.89–0.91 (t, 3 H, CH_3), 0.92–0.98 (m, 1 H, H^c), 1.05–1.12 (m, 1 H, H^b), 1.31–1.45 [m, 6 H, $(CH_2)_3$], 1.61–1.68 (m, 1 H, H^a), 3.85 (s, 3 H, CH_3O), 7.07 (d, 2 H, H^e, H^f), 7.90 (d, 2 H, H^i, H^j); spectrum showed that the product was the pure *trans* isomer; ν_{max}(neat)/cm^{-1} 3000–2870 (m), 1720 (s), 1610 (s), 1440 (s), 1280 (s), 1180 (s), 1110 (s), 770 (s), 700 (s); *m/z* 233 (M + 1, 16%), 232 (M^+, 44), 162 (100), 131 (89), 117 (19), 116 (18), 115 (26), 91 (18), 77 (9) (HRMS for $C_{15}H_{20}O_2$: Calc. 232.1463. Found, 232.1444).

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