Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2809-2812, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00478-4

# Synthesis of Contiguous Cyclopropanes by Palladium-Catalyzed Suzuki-Type Cross-Coupling Reactions.

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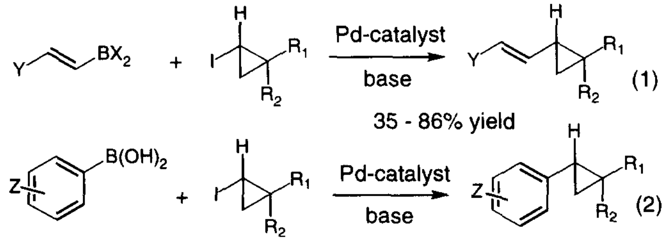
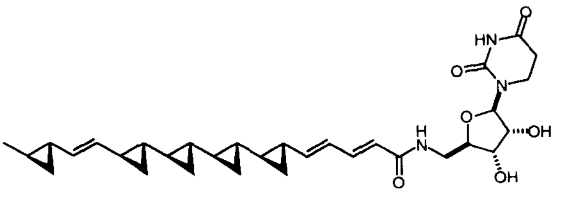
***Abstract:*** Suzuki cross-coupling reactions between a variety of iodocyclopropanes and cyclopropylboronate esters to produce symmetrical or unsymmetrical contiguous cyclopropanes was achieved in good yields. © 1997 Elsevier Science Ltd.

We recently reported the cross-coupling reaction between iodocyclopropanes and vinyl- or arylboronic acids under Suzuki-type conditions (eq 1-2).[1,2] This methodology, that involves insertion of palladium(0) in a cyclopropyl halide bond, increases the scope of the Suzuki-cross coupling reaction to allow preparation of these two classes of compounds.[3,4]



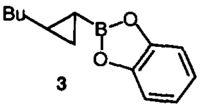
The isolation of two polycyclopropane natural products (**1** and **2**)[5] and the perspective of their syntheses on solid supports[6] led us to evaluate the coupling reaction between two suitably substituted cyclopropyl precursors.[7] Herein, we report the first unsymmetrical coupling of two cyclopropyl units under modified Suzuki conditions.



(-)-FR-900848 (**1**)

(-)-U-106305 (**2**)

Our initial attempts to achieve the coupling involved the reaction between several boronate esters derived from **6** and iodocyclopropane **7**. The starting racemic cyclopropylboronic acid derivatives were readily available by the diazomethane cyclopropanation[8] of the vinyl boronate ester[9,10] obtained by the hydroboration of the corresponding alkyne with catecholborane.[11] The iodocyclopropanes were prepared as previously described.[1] Our first experiment in order to cross-couple **3** and **7** using our previously developed reaction conditions completely failed (Table 1, entry 1). These conditions, which involved using a mixture of DMF-$H_2O$ at 90 °C with $K_2CO_3$ as the base and $Bu_4NCl$ as an additive, led to the decomposition of the iodocyclopropane **7**. As expected, the use of other boronate esters **4** and **5** did not produce any of the desired coupling product (Table 1, entry 2-3). Many other conditions were surveyed using different bases, solvents, and catalysts in order to affect the desired coupling reaction (Table 1, entry 4-12).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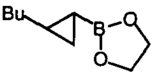
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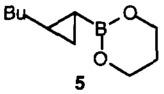

**5**

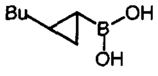
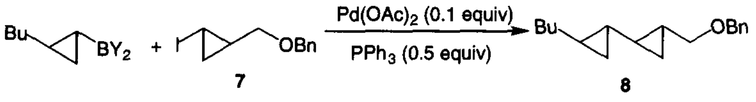

**6**

**Table 1. Various attempts to cross-couple boronate esters and acid 3-6 and iodocyclopropane 7.**[a]



| Entry | Y | Conditions | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **3** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 48 | ---[c] |
| 2 | **4** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 48 | ---[c] |
| 3 | **5** | DMF, $H_2O$, $K_2CO_3$, $Bu_4NCl$ | 20 | ---[d] |
| 4 | **4** | DME, $K_2CO_3$, 80 °C | 90 | ---[d] |
| 5 | **4** | DME, NaOH[e], 80 °C | 90 | 10 |
| 6 | **4** | DME, NaOEt[f], 80 °C | 90 | 30 |
| 7 | **4** | DME, KO*t*-Bu[g], 80 °C | 36 | 65[h] |
| 8 | **5** | Toluene, $K_3PO_4 \cdot 3H_2O$, 100 °C | 48 | ---[d] |
| 9 | **5** | DME, $K_3PO_4 \cdot 3H_2O$, 80 °C | 48 | ---[d] |
| 10 | **3** | DME, KO*t*-Bu[g], 80 °C | 90 | 50 |
| 11 | **5** | DME, KO*t*-Bu[g], 80 °C | 36 | 69 |
| 12 | **6** | DME, KO*t*-Bu[g], 80 °C | 48 | 54 |

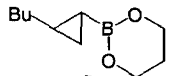
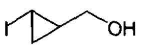
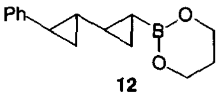
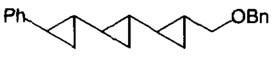
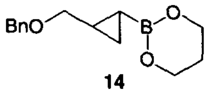
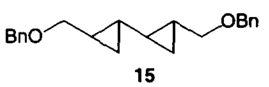
[a] All the reactions were carried out using a mixture of iodocyclopropane (1.0 equiv), the boronate ester or acid (1.1 equiv), $Pd(OAc)_2$ (0.1 equiv), $Ph_3P$ (0.5 equiv) in the appropriate solvent (0.1M). The amount of base used was as follows: Entry 1-3: $K_2CO_3$ (3 equiv) and $Bu_4NCl$ (2 equiv). Entry 4 : $K_2CO_3$ (2 equiv). Entry 8-9: $K_3PO_4 \cdot 3H_2O$ (3 equiv). [b] Isolated yields based on the amount of iodocyclopropane used. [c] Decomposition of the iodocyclopropane was observed. [d] Unreacted starting materials were obtained in these cases. [e] A 2.5M solution of NaOH (3 equiv) in $H_2O$ was used. [f] A 2.0M solution of NaOEt in EtOH (3 equiv) was used. [g] A 2.0M solution of KO*t*-Bu in *t*-BuOH (2 equiv) was used. [h] We also obtained similar yields with $PdCl_2(dppf)$ (59%), $Pd(PPh_3)_4$ (61%) and $PdCl_2(PPh_3)_2$ (55%).

As reported by Chan and Zhang for the cross-coupling reactions involving bulky boronic acids,[12] the nature of the base had a spectacular effect on the efficiency of the coupling. We have also found that a dramatic rate enhancement in the Suzuki coupling of cyclopropylboronate esters and iodocyclopropane was observed in the presence of potassium *t*-butoxide (entry 7). Conversely, the use of weaker bases led to lower yields of the desired dicyclopropane product (entry 4-6). Wang and Deng have recently reported that $K_3PO_4 \bullet 3H_2O$ in toluene was a very effective combination for the cross-coupling reaction of **6** and various aryl halides but these conditions did not lead to any of the desired coupling product (entry 8-9).

Quite interestingly, the nature of the ester group of the boronate ester derivative affected both the rate and yield of the reaction (entry 7, 10-12). It is noteworthy that the best conditions involved using anhydrous solvents. Based on this, it appears that the boronate ester (and not the boronic acid) is the active species that is involved in the coupling process. The increased nucleophilicity of the alkylboronate species using more basic groups on boron appears to play an important role.[13] Based on this observation, the boronate ester derived from 1,3-propanediol was selected as the ester of choice in these reactions since it produced the highest yield of the coupling product with the fastest reaction rate.

These conditions were also effective for the coupling reaction of other cyclopropylboronate ester derivatives with various iodocyclopropanes (Table 2).

**Table 2. Cross-coupling reactions of boronate esters and iodocyclopropane derivatives.**

| Entry | Boronate ester | Iodocyclopropane | time (h) | Product[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | <br> <br>**5** | <br> <br>**9** | 36 | <br> <br>**11** | 64 |
| 2 | <br> <br>**12** | **7** | 48 | <br> <br>**13** | 60 |
| 3 | <br> <br>**14** | **7** | 48 | <br> <br>**15** | 71 |

[a] Compounds **11**, **13**, and **15** were formed as equimolar mixtures of diastereomers. [b] Isolated yield of chromatographically homogeneous product. The products were characterized by $^1H$, $^{13}C$ NMR, IR, elemental analysis and/or HRMS.

**Typical Procedure:** To a mixture of iodocyclopropane **7** (100 mg, 0.35 mmol), boronate ester **5** (70 mg, 0.38 mmol), palladium acetate (8 mg, 0.035 mmol), and triphenylphosphine (46 mg, 0.175 mmol) was added DME (4 mL). The solution was deoxygenated by freeze-thaw techniques and a solution of potassium *t*-butoxide (1M solution in *t*-BuOH, 700 μL, 0.7 mmol) was added. The mixture was then placed in an oil bath at 80 °C and stirred for 36 h. The cooled mixture was then diluted with ether (20 mL) and the organic layer was washed with water (10 mL), sat. aq. NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (2% ether/hexanes) to afford the desired coupled product (62 mg, 69%) as a colorless oil and a 1:1 mixture of diastereomers: $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H, Ph), 4.53 (s, 2H), 3.39-3.33 (m, 1H), 3.30-3.25 (m, 1H), 1.34-1.06 (m, 6H), 0.89 (t over m, $J = 7$ Hz, 3H), 0.92-0.83 (m, 1H), 0.77-0.68 (m, 1H), 0.58-0.52 (m, 1H.), 0.47-0.40 (m, 1H.), 0.35-0.28 (m, 2H,), 0.24-0.19 (m, 1H), 0.17-0.10 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$), 1:1 mixture of diastereomers, δ 138.6, 128.2, 127.5 (2), 127.3 (2), 74.0 (2), 72.2 (2), 33.6, 31.7 (2), 22.3 (2), 19.5 (2), 18.7 (2), 17.2, 16.8, 16.7 (2), 14.0, 10.4, 9.8, 8.6, 8.4. HRMS calcd for $C_{18}H_{26}O$ 258.1984, found 258.1995.

**Acknowledgment.** This research was supported by the NSERC (Canada), Petroleum Research Fund, administered by the ACS, an Alfred P. Sloan Research Fellow, Merck Frosst Canada, F.C.A.R. (Québec) and the Université de Montréal.

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9. The boronate esters **4** and **5** were prepared by mixing the boronic acid resulting from the hydroboration with the appropriate diol (pentane) followed by $CH_2N_2/Pd(OAc)_2$ treatment. Ester **3** was prepared by mixing boronic acid **6** and catechol (pentane).
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13. The rate and yield of the reaction increases as the $pK_a$ ($H_2O$) of the corresponding diol used as the boronate ester increases: catechol: 9.48; ethylene glycol: 14.8-15.1, 1,3-propanediol: 15.1.

(*Received in USA* 13 *February* 1997; *accepted* 4 *March* 1997)