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Palladium-Catalyzed Suzuki-Type Cross-Couplings of Iodocyclopropanes with Boronic Acids: Synthesis of *trans*-1,2-Dicyclopropyl Alkenes

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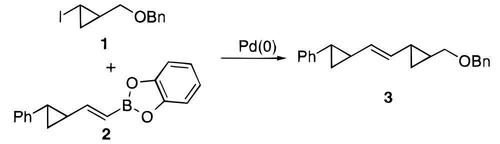
The palladium-catalyzed coupling reaction between boronic acids and alkenyl and aryl iodides is a powerful and general method for the formation of carbon−carbon bonds.[1] The availability of the reagents and the mild reaction conditions all contribute to the versatility of this reaction. The Suzuki coupling offers several additional advantages, such as being largely unaffected by the presence of water and having a broad range of functional groups. Consequently, the coupling reaction has been used extensively in the synthesis of natural products, nucleoside analogs, and pharmaceutical compounds. Although the Suzuki method has been extensively used for the coupling of two sp^2 carbon atoms,[2] it also allows the coupling of carbon atoms of other hybridization.[3] We were interested in extending the Suzuki cross-coupling reaction to cyclopropyl iodides to synthesize more complex cyclopropanes.[4−6] To the best of our knowledge, there is no literature precedent for the oxidative insertion of palladium(0) into a cyclopropyl iodide bond; however, we felt that this process was feasible since cyclopropanes are known to have some sp^2 character.[5] Cross-coupling of vinyl halides and cyclopropylzincs[7] under Negishi's conditions are known, but these reactions rely on the insertion of palladium(0) into the sp^2 vinyl halide bond in the oxidative insertion step of the catalytic cycle. Herein, we report the first palladium-catalyzed cross-couplings of iodocyclopropanes with vinyl boronate esters and aryl boronic acids under Suzuki-type conditions.

For our initial studies, we examined the reaction between iodocyclopropane **1**[8] and vinylboronate ester **2**[9] (Table 1). A satisfying 25% conversion to the cross-coupled product **3** was observed when the precursors **1** and **2** were first submitted to standard Suzuki conditions (entry 1) using sodium carbonate as the base in benzene−water. Increasing the solubility of the base in the organic phase slightly improved the conversion[10] (entries 2 and 3), but the overall yield was still at an impractical level. In order to further increase the solubility of the base in the organic phase, a phase-transfer catalyst was used as an additive. The addition of tetrabutylammonium chloride with cesium carbonate improved the conversion to 50% in both benzene−H_2O or DME−H_2O mixtures (entries 4 and 5). Conversely, using 20% palladium(0) catalyst in benzene−H_2O gave an 80% conversion (entry 6). Many other conditions were surveyed using different bases, solvents, and catalysts in order to optimize the conditions for the coupling. Gratifyingly, quantitative conversion of iodocyclopropane **1** to the desired coupling product **3** was obtained in DMF−H_2O at 90 °C using K_2CO_3 as the base and Bu_4NCl as an additive (entry 7).[11]

Table 1. Effect of Solvent and Base on the Cross-Coupling Reaction



Entry[a]	Solvent	Additive	Conversion[b]
1	Benzene-H_2O (4:1)	Na_2CO_3	25%
2	Benzene-H_2O (4:1)	K_2CO_3	30%
3	Benzene-H_2O (4:1)	Cs_2CO_3	35%
4	Benzene-H_2O (4:1)	Cs_2CO_3 + Bu_4NCl	50%
5	DME-H_2O (4:1)	Cs_2CO_3 + Bu_4NCl	50%
6[c]	Benzene-H_2O (4:1)	K_2CO_3 + Bu_4NCl	80%
7	DMF-H_2O (4:1)	K_2CO_3 + Bu_4NCl	>95%

[a] Reactions were carried out at 90 °C for 20 h using a mixture of iodocyclopropane **1** (0.10 mmol), boronate ester **2** (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.05 mmol), and the additive (0.30 mmol). [b] Conversions were determined by ^1H NMR analysis and are based on the remaining iodocyclopropane **1**. [c] In this case, 0.02 mmol of $Pd(OAc)_2$ is used with 0.10 mmol of PPh_3.

The cross-coupling reaction of a variety of vinyl boronate esters with *cis*- or *trans*-3-iodocyclopropylmethanol derivatives **1**, **4**, and **6** were then carried out using these optimized conditions (Table 2).

High yields of the cross-coupling products were usually obtained with alkyl-substituted vinylboronate esters. In most cases, the reaction was completed in less than 6 h. However, moderate yields and lower reactivities were obtained when the vinyl boronate ester moiety contained an oxygen (entries 4 and 5). The cross-coupling reaction is also applicable to *cis*-iodocyclopropane **6** (entry 3), and it tolerates an unprotected hydroxyl group such as that in **4** (entry 2).

With these results in hand, we next carried out the Suzuki cross-coupling reaction on a variety of aryl- and

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[1] (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A.; Miyaura, N.; Suginome, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2221−2223.

[2] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519.

[3] For examples see: (a) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396−2397. (b) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694. (c) Moriya, T.; Furuuchi, T.; Miyaura, N.; Suzuki, A. *Tetrahedron* **1994**, *50*, 7961−7968. (d) Miyaura, N.; Maeda, K.; Suginome, H.; Suzuki, A. *J. Org. Chem.* **1982**, *47*, 2117−2120.

[4] For examples of coupling reactions involving cyclopropanes, see: (a) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415−2418. (b) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893−894. (c) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075−5078.

[5] For reactivity studies and molecular orbital calculations of cyclopropanes see: (a) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229−234.

[6] (a) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748−754. (b) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629−10634.

[7] (a) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075−5078. (b) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958−2965.

[8] (±)-Iodocyclopropane **1** was prepared by known procedures: (a) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854. (b) Piers, E.; Coish, P. D. *Synthesis* **1995**, 47−55.

[9] Boronate ester **2** was prepared in five steps from cinnamyl alcohol (1. $ZnEt_2$, CH_2I_2; 2. DMSO, $(COCl)_2$, Et_3N; 3. CBr_4, PPh_3; 4. BuLi; 5. catecholborane). See the Supporting Information for details.

[10] It was shown previously that the addition of a base greatly facilitates the cross-coupling of organoboron reagents with electrophiles by accelerating the rate of the transmetalation step; for examples, see: (a) Takayuki, O.; Miyaura, N.; Suzuki, A. *J Org. Chem.* **1993**, *58*, 2201−2208. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419−422.

[11] The coupling yield drops significantly if the addition of Bu_4NCl is omitted. For a detailed discussion of the cross-coupling catalytic cycle, see: (a) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749−1758. (b) Moreno-Manas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346−2351 and references cited therein.

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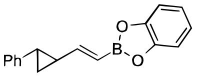
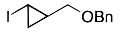
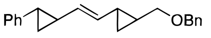
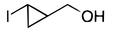
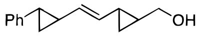
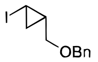
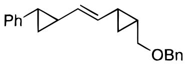
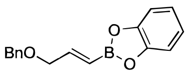
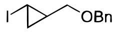
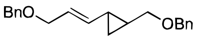
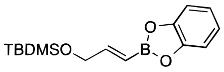
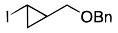
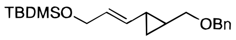
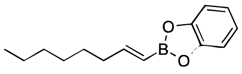
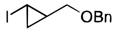
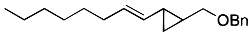
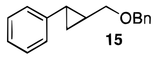
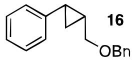
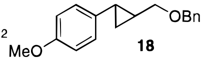
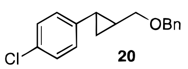
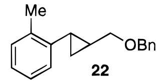
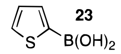
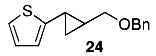
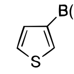
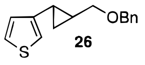
Table 2. Cross-Coupling Reactions of Vinyl Boronate Esters with Iodocyclopropanes

Entry[a]	Boronate Ester	Iodocyclopropane	time (h)	Coupled Product	Yield[b]
1	 2	 1	6	 3	84%
2		 4	6	 5	81%
3		 6	6	 7	82%
4	 8		20	 9	64%
5	 10		20	 11	35%
6	 12		6	 13	86%

[a] All the reactions were carried out at 90 °C in DMF−H_2O (4:1) using a mixture of the iodocyclopropane (0.40 mmol), the boronate ester (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), PPh_3 (0.20 mmol), K_2CO_3 (1.20 mmol), and Bu_4NCl (0.80 mmol). [b] Isolated yields.

Table 3. Cross-Coupling Reactions of Arylboronic Acids[a]

Entry	Boronic acid	Product	Yield (%)[b] (method)[c]
1	$PhB(OH)_2$ **14**	 15	80% (A)
2	$PhB(OH)_2$ **14**	 16	78% (A)
3	p-$MeOC_6H_4B(OH)_2$ **17**	 18	85% (A)
4	p-$ClC_6H_4B(OH)_2$ **19**	 20	83% (A)
5	o-$MeC_6H_4B(OH)_2$ **21**	 22	15% (A) 80% (C)
6	 23	 24	0% (A) 20% (B) 70% (C)
7	 25	 26	42% (B) 78% (C)

[a] Coupling reactions were conducted at 90 °C for 4−20 h using the iodocyclopropane (0.40 mmol), the boronic acid (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), and PPh_3 (0.20 mmol). [b] Conditions used are as follows. Procedure A: K_2CO_3 (1.20 mmol), Bu_4NCl (0.80 mmol) in DMF−H_2O (4:1). Procedure B: K_2CO_3 (1.20 mmol), Bu_4NCl (0.80 mmol) in DME−H_2O (4:1). Procedure C: CsF (1.80 mmol) in anhyd DMF. [c] Isolated yield.

heterocyclic-derived boronic acids (Table 3).[12] Phenylboronic acid (**14**) gave very good coupling yields with both the *trans*- and *cis*-iodocyclopropane **1** and **6** (entries 1 and 2). *p*-Substituted arylboronic acids were also smoothly converted into the coupling products in high yields (entries 3 and 4). One limitation of the coupling reaction under these conditions surfaced when we attempted to use *o*-substituted arylboronic acids. For example, the coupling reaction using 2-methylphenylboronic acid gave the desired compound in only 15% yield.[13] The addition of fluoride ion is known to facilitate the cross-coupling process via the possible formation of a stable trifluoroborate intermediate in the transmetalation step.[14] In our case, the addition of CsF afforded the *o*-methylphenyl-substituted cyclopropane product **22** in 80% isolated yield (entry 5). Attempts to cross-couple heterocyclic-derived boronic acids such as 2-thienylboronic acid under the initial conditions (K_2CO_3, Bu_4NCl) completely failed and resulted in the exclusive formation of the deboronation product.[15] Gronowitz[16] has shown that the use of DME as the solvent was another means of preventing the formation of the deboronation product. The desired coupled products **24** and **26** were obtained in moderate yields when DME was used as the solvent. The DMF−CsF combination again produced the best results, affording the desired coupled products in 70 and 78% isolated yield (entries 6 and 7).

In conclusion, we have reported the first cross-coupling reaction of substituted cyclopropyl iodides with boronic acids. This methodology represents the first insertion of palladium(0) in a cyclopropyl halide bond, and it opens the door to other palladium-catalyzed coupling reactions involving cyclopropyl iodides.

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Supporting Information Available: General experimental procedures, characterization data for all compounds, and copies of the ^1H and ^{13}C NMR spectra of the reaction products (50 pages).

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(12) For the preparation of arylboronic acids see: Thompson, W.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237−5243.

(13) For examples of cross-coupling studies of *o*-substituted phenylboronic acids see: (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210. (b) Anderson, J. C.; Namli, H. *Synlett* **1995**, 765−766. (c) Zhang, H.; Chan, K. S. *Tetrahedron Lett.* **1996**, *7*, 1043−1044.

(14) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(15) Minor amounts of thiophene could be detected in the crude NMR of the reaction mixture.

(16) Gronowitz, W. J.; Bobosic, V.; Lawitz, K. *Chem. Scripta* **1984**, *23*, 120−125.-