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Cyclopropylboronic acid: synthesis and Suzuki cross-coupling reactions

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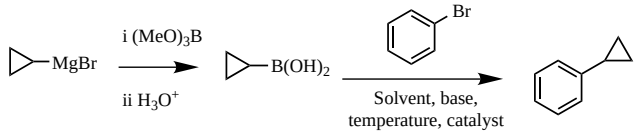
Abstract—An efficient synthesis of cyclopropylboronic acid is reported. This compound undergoes efficient Suzuki-type coupling reactions with a range of aryl and heteroarybromides.

The cyclopropyl group is an increasingly common structural motif in pharmaceutically active molecules and is frequently included as a substituent in structure activity relationship studies.[1] As part of a current drug discovery program in our laboratories we required an efficient and general method for introduction of unsubstituted cyclopropyl groups to aromatic and heteroaromatic compounds. The synthesis of such compounds usually relies on the cyclopropanation of the related vinyl compound by diazomethane,[1b] sulfoxonium ylid chemistry[2] or other methods.[3] Direct introduction of the cyclopropyl ring can be achieved using Negishi[4] or Kumada[5] type couplings of organozinc and Grignard reagents, but these procedures would not be compatible with all functionalities. Alternatively, the Stille-coupling of cyclopropyl(tri-*n*-butyl)stannane with a limited range of substrates has been reported.[6,7]

In recent years the palladium-catalyzed Suzuki cross-coupling reaction of organoboranes with halides or triflates has evolved into an efficient and mild method for carbon–carbon bond formation that is tolerant of many functional groups.[8] In many cases boronic acids are isolable, air- and moisture-stable compounds which can be stored at room temperature prior to use as required, and we felt this would be a suitable procedure for our needs. Indeed, the groups of Deng[9] and Marsden[10] have both reported successful cross-coupling reactions of *substituted* cyclopropylboronic acids with bromoarenes and acrylates. Carboni et al. have prepared the pinacol boronate esters of cyclopropylboronic acid and substituted derivatives; however, no coupling reactions were reported.[11] In all these procedures the boronic acids or esters were prepared by cyclopropanation of the related vinyl compounds, which in turn had to be prepared. Recently, Soderquist has also demonstrated the coupling reactions of B-cyclopropyl-9-BBN, which was prepared via a circuitous route and used in situ.[12] However, we were unable to find any reports concerning the preparation or use of unsubstituted cyclopropylboronic acid, and we set out to explore the possibility of utilizing this reagent.[13,14]

We elected to prepare the boronic acid via reaction of cyclopropyl Grignard rather than attempt to cyclopropanate vinylboronic acid. Hence, addition of a THF solution of commercially available cyclopropylmagnesium bromide to a slight excess of trimethylborate at low temperature followed by slow warming to room temperature and acidic quench gave a solution of the desired boronic acid (Scheme 1). Ethereal solvents were found to be the most efficient for removing the acid from the aqueous layers and the boronic acid was isolated as a white solid in 55% yield by trituration of the crude mixture.[15] The product typically contained 5–10% of boric acid (^{11}B NMR), which did not prove to be detrimental to the following Suzuki reactions. The acid was stored in a capped vial at room temperature, without noticeable decomposition or loss of activity over a period of several months.



Scheme 1.

Keywords: cyclopropylboronic acid; Suzuki cross-coupling; pharmaceutically acitve molecules.

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Table 1. Suzuki coupling of cyclopropylboronic acid with bromobenzene

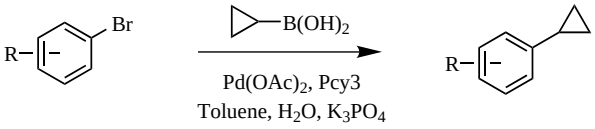
Solvent	Temperature (°C)	Base	Catalyst	Assay yield % (6 h)
Toluene	100	K_3PO_4	$Pd(PPh_3)_4$	40
DME	80	K_3PO_4	$Pd(PPh_3)_4$	27
THF	65	K_2CO_3	$Pd(PPh_3)_4$	25 (48 h)
Toluene	100	K_3PO_4	$PdCl_2dppf$	40
Toluene/H_2O	100	K_3PO_4	$Pd(PPh_3)_4$	58
Toluene/H_2O	100	K_3PO_4	$Pd(OAc)_2/Pcy_3$	91

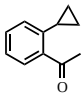
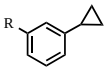
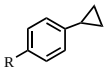
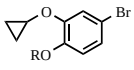
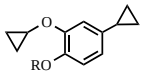
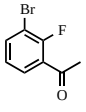
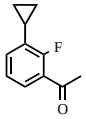
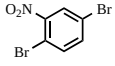
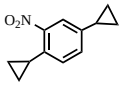
The reaction of cyclopropylboronic acid with bromobenzene was chosen to screen conditions. Reactions were run using 1.2 equiv. of the boronic acid and monitored by HPLC after 6 h (Scheme 1 and Table 1). Our optimum conditions were similar to those utilized by Deng;[9] however, we found that the addition of water to the reaction had a significant accelerating affect and that the bulky tricyclohexylphosphine (Pcy_3) ligand (10 mol%) in conjunction with palladium acetate (5 mol%) gave the best conversion.

The scope of the reaction with aryl bromides was explored using these optimized conditions (Table 2). Using 1.3 equiv. of the boronic acid the coupling proceeds smoothly with 2-, 3-, 4- and polysubstituted aryl bromides and was found to be tolerant of ketone, ester, aldehyde, amine, nitrile, fluoro and ether functionalities, although no reaction with the phenol was seen (entry 6).[16,17] Additionally, a dibromide gave the double Suzuki product in moderate yield (60%, entry 9) along with the product resulting from a single coupling of the *ortho*-bromine.

Coupling of the boronic acid with heteroaromatic and other bromides was also studied (Table 3). Substrates including pyridines,[18] quinolines and a furan gave good yields of the desired products as did 2-bromonaphthoquinone (entry 6) and a vinyl bromide (entry 7). However, cyclopropylboronic acid did not react with chlorobenzene, 1-chloro-4-nitrobenzene or phenyl triflate using the current reaction conditions. The Buchwald conditions recommended for Suzuki couplings of aryl chlorides were also explored.[19] Coupling of the boronic acid with 1-chloro-4-nitrobenzene gave a 20% yield of the required product after 24 h, but only trace amounts of product were seen in the reaction with 4-chlorobenzaldehyde after 48 h.[20]

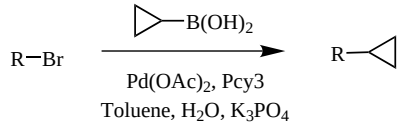
Table 2. Suzuki coupling of cyclopropylboronic acid with aryl bromides

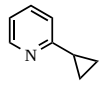
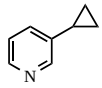
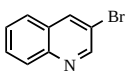
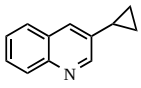
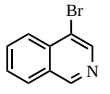
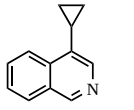
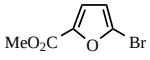
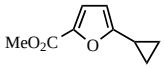
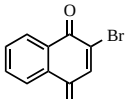
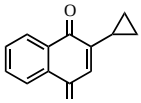
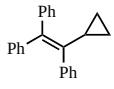


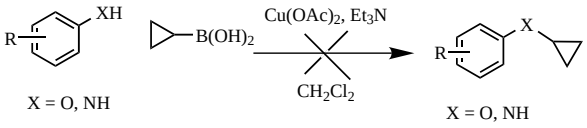
Entry	Starting material	Product	Yield[a]
1			65
2: R = OMe 3: R = NH_2			R = OMe: 95 R = NH_2: 85
4: R = CHO 5: R = CN			R = CHO: 91 R = CN: 96
6: R = H 7: R = Ac			R = H: 0 R = Ac: 83
8			90
9			60

[a] Isolated yield after chromatography

Table 3. Suzuki coupling of cyclopropylboronic acid with other substrates



Entry	Starting material	Product	Yield
1			49
2			76
3			95
4			95
5			81
6			73
7			97



Scheme 2.

Finally, no reaction with phenols or amines was seen using the recently published copper-catalyzed coupling methods of Chan and Evans (Scheme 2).[21]

In conclusion, we have demonstrated that cyclopropylboronic acid can be prepared in good yield by straightforward reaction of the related Grignard reagent with trimethylborate. The boronic acid is air and water stable and participates in Suzuki-type coupling reactions with a range of aryl, heteroaryl and vinyl bromides to give the cyclopropyl adducts in good to excellent yields. Further studies on the use of this reagent and in particular optimization of the coupling with aryl chlorides are underway in our laboratories.

Acknowledgements

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1. For example, see: (a) Todo, Y.; Takagi, H.; Iino, F.; Fukuorka, Y.; Ikeda, Y.; Tanaka, K.; Saikawa, I.; Narita, H. *Chem. Pharm. Bull.* **1994**, *42*, 2049; (b) Turner, W. R.; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 281.
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13. A report exists claiming cyclopropylboronic acid cannot be made, see: Ref. 6a.
14. Since completion of this work the use of cyclopropylboronic acid for a single cross-coupling reaction has appeared in the patent literature. The boronic acid was not isolated and no yields or data were given. See: Stolle, A.; Dumas, J. P.; Carley, W.; Coish, P. D. G.; Magnuson, S. R.; Wang, Y.; Nagarathnam, D.; Lowe, D. B.; Su, N.; Bullock, W. H.; Campbell, A.-M.; Qi, N.; Baryza, J. L.; Cook, J. H. Substituted indoles, pharmaceutical compositions containg such indoles and their use as PPAR-γ binding agents. International patent WO 2002030895, April 18, 2002.
15. To a stirred, cooled (−78°C) solution of trimethylborate (2.2 mL, 19.5 mmol) in THF (8.0 mL) was added cyclopropylmagnesium bromide (30.0 mL, 0.5 M in THF, 15.0 mmol) dropwise, which led to formation of a white precipitate. After 1 h the reaction was warmed to room temperature and stirred for a further 6 h. Aqueous HCl (20 mL, 2.0N) was added and the mixture stirred for 1 h, then washed with dichloromethane (15 mL). The dichloromethane layer was back extracted with water (2×15 mL) and the aqueous fractions combined and extracted with MeO*t*Bu (4×40 mL). The combined organics were dried over $MgSO_4$ and concentrated to give a crude white solid which was isolated by trituration with CH_2Cl_2/hexanes to give 0.72 g (56%) of a white solid; mp (H_2O) 92–93°C; ^1H NMR (500 MHz, CD_3OD): δ 0.53 (2H, m), 0.48 (2H, m), −0.14 (1H, m); ^1H NMR (400 MHz, DMSO-d_6): δ 7.32 (2H, s), 0.40 (2H, m), 0.30 (2H, m), −0.41 (1H, m). ^{13}C NMR (125.7 MHz, CD_3OD): δ 4.18, −5.31 (very broad); ^{11}B NMR (160.4 MHz, CD_3OD): δ 34.3.
16. New compounds gave satisfactory NMR, IR and HRMS or microanalytical data.
17. The reaction in entry 7 is typical. To a solution of aryl bromide (242 mg, 0.894 mmol), boronic acid (100 mg, 1.16 mmol), potassium phosphate (663 mg, 3.13 mmol) and tricyclohexylphosphine (25.0 mg, 0.0894 mmol) in toluene (4.0 mL) and water (200 μL) under a nitrogen atmosphere was added palladium acetate (10.0 mg, 0.0447 mmol). The mixture was heated to 100°C for 3 h and then cooled to room temperature. Water (10 mL) was added and the mixture extracted with EtOAc (2×15 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (10% EtOAc in hexanes) afforded the desired compound as a colorless oil (177 mg, 83%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (1H,

d, $J=1.9$ Hz), 6.90 (1H, d, $J=8.1$ Hz), 6.60 (1H, dd, $J=8.1$, 1.9 Hz), 3.78 (1H, m), 2.27 (3H, s), 1.91 (1H, m), 0.97 (2H, m), 0.78 (4H, m), 0.71 (2H, M); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.1, 150.2, 142.8, 137.4, 122.3, 117.8, 112.3, 51.3, 20.6, 15.4, 9.1, 6.3; IR (thin film) 1765, 1601, 1512, 1491 cm^{-1}; MS (CI) 189 (20, $M-CH_3CO^+$), 161 (100), 133 (20). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.11; H, 6.75%.

18. 2-Bromopyridine gave a 50% yield of bipyridine. The reaction with 3-bromopyridine was complete by LC analysis, but product volatility resulted in a reduced isolated yield.
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20. Reactions were run with 2-(di-*tert*-butylphosphino)biphenyl (10 mol%), palladium acetate (5 mol%), potassium fluoride (3 equiv.) in THF at 45°C.
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