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Enantiomerically Pure Cyclopropane Building Blocks: Synthesis and Transformations of 2-Iodocyclopropylboronic Esters

Erwin Hohn, Jörg Pietruszka*

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (+49)-711-685-4335, e-mail: joerg.pietruszka@po.uni-stuttgart.de

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Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Abstract: Enantiomerically pure 2-iodocyclopropylboronic esters **6** and **8** have been synthesized from the readily available allylic alcohol **2** *via* an oxidation-radical decarboxylation sequence. These unique building blocks have been demonstrated to be versatile intermediates for a consecutive Suzuki-coupling with aryl-, heteroaryl-, alkenyl-, and cyclopropylboron derivatives (1 example each).

Keywords: boron; chiral auxiliaries; cross-coupling; cyclopropanes; palladium

Introduction

Despite the fact that the chemistry around the cyclopropane moiety is an old field of research, it still is a flourishing field with many new aspects and applications continuously being published. Accordingly, cyclopropanes have been the center of interest in a recent thematic issue of *Chemical Reviews*.[1] Nevertheless, although some efforts were directed towards truly general sequences to enantiomerically pure cyclopropanes, no such protocol has been disclosed as yet.[2] The utilization of cyclopropylboronic esters could be a promising approach,[3–10] with many transformations of the boron moiety possible. A difficulty used to be the lack of stability of boronates thus preventing the supply of enantiomerically pure intermediates.[11–15] We recently introduced esters of the general type **1**[16–20] (as well as higher substituted[21,22] and *cis*-configurated[23] derivatives) that proved to be highly stable, allowing for chromatographic purification and separation of the diastereoisomers (Figure 1). All products were found to be solids which made them convenient to handle and – from the practical point of view another important issue – very easy to detect due to the chromophore in the auxiliary. In addition, we proved that a number of envisaged transformations were not only possible *via* the boronate, but also selectively in the side chain. In this context, we have shown in a number of investigations the convenience of alcohol **2**.[17,18] However, in order to have a truly flexible building block, we pursued the synthesis of a cyclopropane **3** that would ultimately allow us to use the synthetic potential of boron. More importantly, in a first step we should be able to substitute a suitable group 'X' preferentially *via* a palladium-catalyzed cross-coupling (1st transformation) without touching the borolane unit of **3**. Only a consecutive step (2nd transformation) should lead to its substitution *via* established reactions. In the present communication we present the initial results of our search for such enantiomerically pure 1,2-disubstituted cyclopropanes.

Results and Discussion

Our initial targets were halocyclopropanes **3** (X = halide). The starting material of our investigation, alcohol **2**, is readily available in high yield from the silyl-protected propargyl alcohol **4** *via* a hydroboration-deprotection-cyclopropanation sequence (Scheme 1).[17,18] Direct oxidation to carboxylic acid **5** was conveniently achieved by a ruthenium-catalyzed reaction (yield: 90%). Next, we focused on the thermal decarboxylation of the corresponding Barton thiohydroxamic ester[24] in the presence of iodoform, a sequence that was successfully applied (in the presence of bromoform) by Falck et al. in their synthesis of the oligocyclopropane antibi-

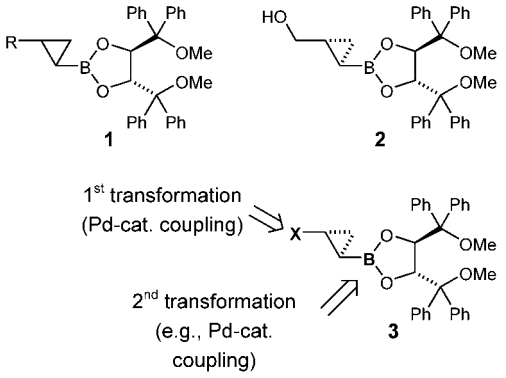

Figure 1. Flexible use of stable, enantiomerically pure cyclopropylboronic esters.

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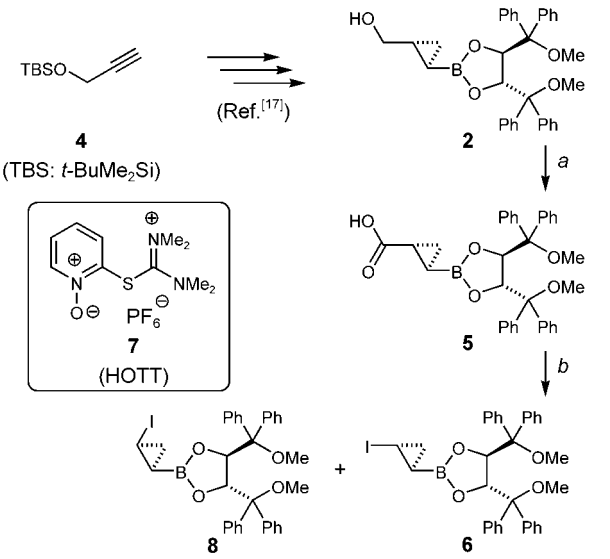
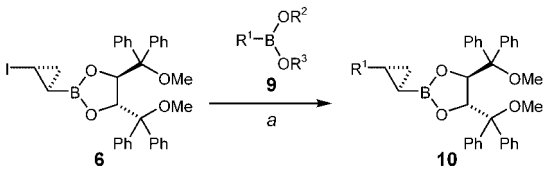
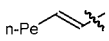
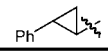


Scheme 1. Synthesis of iodocyclopropanes **6** and **8**. Conditions: a) $NaIO_4$, cat. $RuCl_3 \cdot 3\,H_2O$, $CCl_4/H_2O/MeCN$, 2 h, 40 °C (90%); b) 1. 1.2 equivs. **7**, cat. DMAP, MeCN/THF, Et_3N, 1 h, rt; 2. cyclohexene, 3 equivs. HCI_3, 24 h, 80 °C (70% of **6** and **8** as a separable 6:1 mixture).



Entry	R^1	R^2,R^3	Yield
a	Ph-	H,H	87%
b		H,H	79%
c		H,H	65%
d		-$(CH_2)_3$-	67%

Scheme 2. Suzuki couplings of iodocyclopropane **6**. Conditions: a) 1.5 equivs. **9**, 2 equivs. KO*t*-Bu (1 M in *t*-BuOH), 0.05 equivs. $Pd(PPh_3)_4$, DME, 15 h, 80 °C.

otic FR-900848.[25,26] We observed low yields for the formation of iodide **6** when we introduced the ester *via* the acid chloride (33%). Direct esterification using DCC (dicyclohexylcarbodiimide) proved unsatisfactory as well. Again, not the consecutive radical reaction was problematic, but the formation of side-products during the first step that could not be separated after workup. The method of choice giving pure products in good overall yield was based on recent work by Garner et al.[27] The group introduced the 'HOTT-reagent' **7** to efficiently synthesize the Barton thiohydroxamic ester. The following radical transformation yielded the desired iodide **6** as well as the *cis*-cyclopropane **8** as a 6:1 mixture in 70% yield. The isomers were readily separated by chromatography.

We then focused on the transformation of the major isomer **6** with boron derivatives **9** (Scheme 2). Surprisingly, despite the fact that iodocyclopropanes are readily available (e.g., ref.[28,29]), only a limited number of palladium-catalyzed cross-couplings have been reported.[7,18,30,31] We were pleased to find that different palladium sources successfully led to the formation of product **10**, however, of ultimate importance for a high turnover was a) the absence of oxygen during the reaction and b) the purity of all reagents – catalysts and iodide **6**. In our hands, the conditions used by Hildebrand and Marsden[8] were most convenient. We observed a dramatic decrease in yield (35–70%) when using only one equivalent of boron derivative **9** and as a compromise between best yield and efficient use of boronic acid/ester **9**, 1.5 equivalents of **9** were introduced. These standard conditions would allow not only the cross-coupling with phenylboronic acid (**9a**) (87% of **10a**), but also with heteroarylboronic acids (e.g., **9b**: 79% of **10b**), alkenylboronic acids (e.g., **9c**: 65% of **10c**), and especially cyclopropylboronates (e.g., **9d**: 67% of **10d**). This is only the second[30] example for a successful cyclopropane-cyclopropane cross-coupling using a palladium catalyst. In the present case we still have the advantage to be able to further elaborate the bicyclopropane *via* the intact boron moiety.[18]

Although the *cis*-iodocyclopropane **8** is only the minor product in the radical process (see Scheme 1), it is of importance, since *cis*-cyclopropylboronic esters[23,32] – let alone enantiomerically pure representatives[23] – have hardly been reported yet. In view of the incomplete assignment of the absolute configuration of most derivatives,[23] a successful Suzuki–Miyaura coupling[33,34] of compound **8** (with known absolute configuration) could confirm the previous NMR-based results. Fortunately, the reaction between *cis*-iodide **8** and phenylboronic acid (**9a**) not only proceeded more rapidly than with the corresponding *trans*-cyclopropane **6**, but also furnished highly pure product **11** in comparable yield (88%). The comparison of NMR data proved our assignment that was additionally unequivocally supported by the first successful X-ray crystallographic analysis of a *cis*-cyclopropylboronic ester (Scheme 3).

Conclusion

We have reported a short synthesis of 2-iodocyclopropylboronic ester **6** (along with minor amounts of *cis*-derivative **8)**, a promising new, enantiomerically pure cyclopropane building block. It was demonstrated that the iodide could be successfully introduced into palladi-

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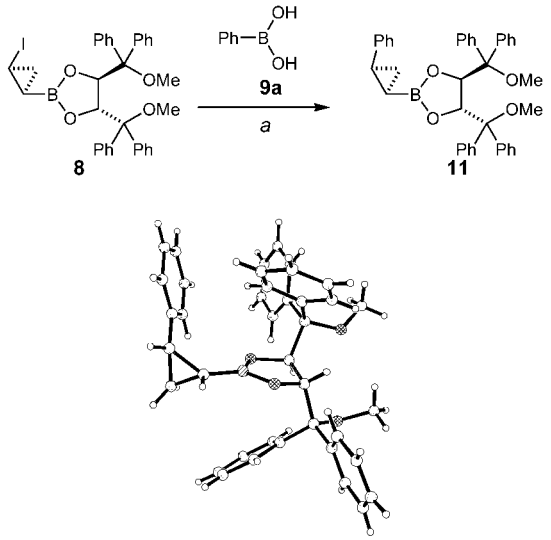

Scheme 3. Suzuki coupling of iodocyclopropane **8**. Conditions: a) 1.5 equivs. **9a**, 2 equivs. KO*t*-Bu (1 M in *t*-BuOH), 0.05 equivs. $Pd(PPh_3)_4$, DME, 15 h, 80 °C (88%).

um-catalyzed cross-couplings with boron compounds, also allowing a cyclopropane-cyclopropane bond formation. Hence, we tuned the reactivity of the coupling partners by varying the protection group on the boronic acid. The process should be rather general and readily applicable for the synthesis of enantiomerically pure 1,2-disubstituted cyclopropanes.

Experimental Section

General Procedure for the Suzuki Coupling

Iodocyclopropane **6** (or **8**) (1.0 equiv.) was dissolved in 1,2-dimethoxyethane (DME; 10 mL/mmol **6** or **8**, respectively). After addition of boron derivative **9** (1.5 equivs.), $Pd(PPh_3)_4$ (5 mol %) and KO*t*-Bu (2 mL/mmol **7** of a 1 M solution in *t*-BuOH) the educts were carefully deoxygenated by the freeze technique. After 15 h at 80 °C the mixture was diluted with diethyl ether, filtered through Celite, rinsed with diethyl ether; the solvents were removed under reduced pressure. All crude products were purified by means of flash column chromatography (petroleum ether:ethyl acetate 99:1).

2-Phenylcyclopropylboronic ester 10a: Data in full agreement with those published.[16]

2-Thienylcyclopropylboronic ester 10b: Softening range: 93–101 °C; $[\alpha]_D^{21}$: −124 (c 0.9, $CHCl_3$); IR (film): ν = 3075, 3056, 2935, 2836, 1450, 1423, 1360, 1241, 1185, 1071, 963, 755 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 586 (3) [M^+], 555 (9) [$(M-CH_3OH)^+$], 197 (100) [$(Ph_2COCH_3)^+$], 105 (13) [$C_7H_5O^+$], 82 (15) [$C_4H_3S^+$], 77 (5) [$C_6H_5^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = −0.18 (ddd, $^3J_{1',3'b}$ = 9.8 Hz, $^3J_{1',3'a}$ = 6.6 Hz, $^3J_{1',2'}$ = 5.4 Hz, 1H, 1′-H), 0.41 (ddd, $^3J_{2',3a'}$ = 8.0 Hz, $^3J_{1',3'a}$ = 6.6 Hz, $^3J_{3'a,3'b}$ = 3.5 Hz, 1H, 3′-H_a), 0.71 (ddd, $^3J_{1,3'b}$ = 9.8 Hz, $^3J_{2',3'b}$ = 5.1 Hz, $^3J_{3'a,3'b}$ = 3.5 Hz, 1H, 3′-H_b), 1.83 (ddd, $^3J_{2',3'a}$ = 8.0 Hz, $^3J_{1',2'}$ = 5.4 Hz, $^3J_{2',3'b}$ = 5.1 Hz, 1H, 2′-H), 2.99 (s, 6H, OCH_3), 5.24 (s, 2H, 4-H, 5-H), 6.66 (dd, ^3J = 5.1 Hz, *J* = 2.2 Hz, 1H, thiophene H), 6.73 (d, *J* = 2.2 Hz, 1H, thiophene H), 7.01 (d, *J* = 5.1 Hz, 1H, thiophene H), 7.25–7.40 (m, 20H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 5.1 (C-1′), 15.3 (C-3′), 21.9(C-2′), 51.6 (OCH_3), 77.1 (C-4, C-5), 83.3 (CPh_2OCH_3), 122.0, 122.6, 127.1, 127.2, 127.4, 127.7, 128.1, 128.3, 138.3 (arom. *C*), 141.2, 141.3 (arom. *i*-C); anal. calcd. for $C_{37}H_{35}BO_4S$ (586.55 g/mol): C 75.76, H 6.01; found: C 75.49, H 5.93.

2-(2-Hepten-1-yl)cyclopropylboronic ester 10c: Softening range: 98–107 °C; $[\alpha]_D^{21}$: −63.5 (*c* 1.45, $CHCl_3$); IR (film): ν = 3060, 2956, 2932, 2833, 1493, 1446. 1421, 1366, 1320, 1239, 1184, 1075, 1032, 1019, 965, 921, 921, 857 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 600 (1) [M^+], 569 (7) [$(M - CH_3OH)^+$], 197 (100) [$(Ph_2COCH_3)^+$], 105 (10) [$C_7H_5O^+$], 97 (4) [$C_7H_{13}^+$], 77 (6) [$C_6H_5^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = −0.47 (ddd, $^3J_{1',2'}$ = 9.8 Hz, $^3J_{1',3'b}$ = 6.5 Hz, $^3J_{1',3'a}$ = 5.3 Hz, 1H, 1′-H), 0.29 (ddd, $^3J_{2',3'a}$ = 7.8 Hz, $^3J_{1',3'a}$ = 5.3 Hz, $^3J_{3'a,3'b}$ = 3.4 Hz, 1H, 3′-H_a), 0.39 (ddd, $^3J_{2',3'b}$ = 9.8 Hz, $^3J_{1',3'b}$ = 6.5 Hz, $^3J_{3'a,3'b}$ = 3.4 Hz, 1H, 3′-H_b), 0.91 (t, $^3J_{6'',7''}$ = 7.2 Hz, 3H, 7″-H), 1.17–1.27 (m, 1H, 2′-H), 1.28–1.36 (m, 6H, 4″-H, 5″-H, 6″-H), 1.95 (m, 2H, 3″-H), 2.99 (s, 6H, OCH_3), 4,79 (dt, $^3J_{1'',2''}$ = 15.1 Hz, $^3J_{2'',3''}$ = 8.5 Hz, 1H, 2″-H), 5.25 (s, 2H, 4-H, 5-H), 5.51 (dd, $^3J_{4',5'}$ = 15.1 Hz, $^3J_{3',4'}$ = 6.9 Hz, 1H, 1″-H), 7.27–7.34 (m, 20H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 1.8 (C-1′), 12.4 (C-7″), 12.9 (C-3′), 16.7 (C-6″), 21.0 (C-5″), 22.1 (C-4″), 27.2 (C-2′), 31.8 (C-3″), 51.7 (CPh_2OCH_3), 77.4 (C-4 and C-5), 83,2 (CPh_2OCH_3), 127.1, 127.2, 127.4, 127.7, 128.1, 128.3, (arom. *C*H), 129.6 (C-1″), 133.4 (C-2″), 141.1, 141.3 (arom. *i*-C); anal. calcd. for $C_{40}H_{45}BO_4$ (600.59 g/mol): C 79.99, H 7.55; found: C 79.63, H 5.33.

2-(2-Phenylcycloprop-1-yl)cyclopropylboronic ester 10d: IR (film): ν = 3057, 3024, 2937, 2832, 1494, 1445, 1423, 1396, 1350, 1320, 1240, 1184, 1074, 1032, 966, 883 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 620 (2) [M^+], 589 (6) [$(M-CH_3OH)^+$], 197 (100) [$(Ph_2COCH_3)^+$], 105 (10) [$C_7H_5O^+$], 77 (5) [$C_6H_5^+$]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = −0.66–0.71 (m, 1H, 1′-H), 0.02–0.05 (m, 1H, 3′-H_a), 0.21–0.25 (m, 1H, 3′-H_b), 0.57–0.61 (m, 1H, 1″-H), 0.63–0.67 (m, 1H, 2′-H), 0.93–0.95 (m, 1H, 3″-H_a), 0.98–1.04 (m, 1H, 3″-H_b), 1.46–1.50 (m, 1H, 2″-H), 2.99 (s, 6H, OCH_3), 5.25 (s, 2H, 4-H, 5-H), 7.17–7.34 (m, 25H, arom. H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −1.9 (C-1′), 10.2/10.4 (C-3″), 13.4 (C-3′), 19.7 (C-2′), 21.6 (C-1″), 25.3/25.4 (C-2″), 51.7 (OCH_3), 77.5 (C-4, C-5), 83.3 (CPh_2OCH_3), 125.2, 125.6, 127.1, 127.2, 127.4, 127.7, 128.1, 128.3, 128.7, 129.3 (arom. *C*), 141.2, 141.3, 143.5 (arom. *i*-C); anal. calcd. for $C_{42}H_{41}BO_4$ (620.31 g/mol): C 81.29, H 6.66; found: C 81.11, H 6.48.

2-Phenylcyclopropylboronic ester 11: Data in full agreement with those published.[23]

X-Ray Crystallographic Data

Crystals of **11** suitable for a crystallographic study were obtained from petroleum ether/diethyl ether at −20 °C. X-ray data were collected on a Siemens P 4 diffractometer with graphite monochromator in Omega scan modus with Cu-K_α (λ = 1.54178 Å) radiation: $C_{39}H_{37}BO_4$, M_r = 580.5, colorless, *T* = 293, crystal size 0.15 × 0.10 × 0.10, triclinic, *P*1, *a* = 9.1714(12) Å, *b* = 9.5155(8) Å, *c* = 11.0476(8) Å, α = 72.611(8)°, β = 77.442(8)°, γ = 62.110(10)°, *V* = 809.75(14) Å^3, *Z* = 1, $d_{calcd.}$ = 1.190 g cm^{-3}, μ = 0.591 mm^{-1}, *F*(000) = 308, θ

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range 4.21–65.99°, 2904 measured/independent reflections, 2299 with [$I > 3\sigma(I)$]. Solved by direct methods and refined by full-matrix, least-squares on F^2 for all data weights to $R = 0.065$, $R_w = 0.164$, S = 1.073, H atoms riding, max. shift/error < 0.001, residual $\rho_{max} = 0.207$ Å^{-3}.

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-230792. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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