Diastereoselective Synthesis of Cyclopropyl Boronic Esters

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Abstract: The conversion of simple 1-alkynes to optically active 2-alkyl-cyclopropan-1-ols is conveniently achieved by a simple protocol. The key step is the cyclopropanation of alkenyl boronic esters derived from (+)-diisopropyl L-tartrate and alkenyl boronic acids. It has been found that best yields could be obtained using diazomethane and palladium(II) acetate as catalyst. The systematic investigation of parameters influencing this reaction led to an improvement of the diastereoselectivity of the transformation.

The cyclopropane moiety is not only ubiquious in natural products, but is also recognized to exhibit important physiological properties.[1] In addition, the versatility of cyclopropanes and their derivaties as building blocks in organic synthesis has been ample demonstrated.[2] Therefore, considerable interest has recently been focused on their enantio- and diastereoselective synthesis.[3] Although a plethora of elegant methods is known and despite very successful protocols for the asymmetric synthesis of cyclopropanes,[4] it is still a major goal to develop a truly general method.[5]

We envisaged that cyclopropyl boronates **1-4** (Figure 1) are potentially the desired building blocks to form a wide-range of different 1,2-disubstituted cyclopropanes in enantiomerically pure form. Their direct transformation to the synthetically versatile cyclopropanols is well established.[6,7] A Suzuki-type coupling of racemic cyclopropyl boronates with aryl halides has been achieved.[8] The introduction of other functional groups and/or the formation of new C-C bonds should also be feasible.[9]

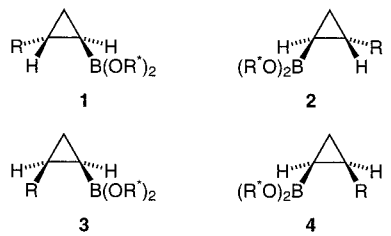
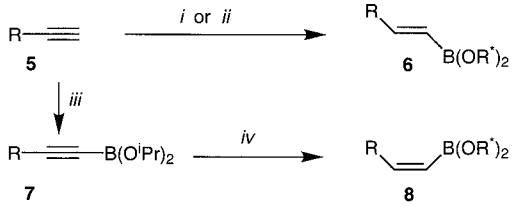


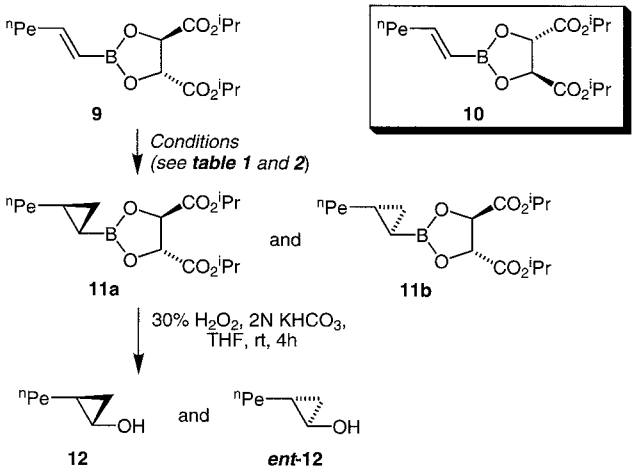
Figure 1

The synthesis of cyclopropyl boronates **1-4** was straight forward. 1-Alkynes **5** can be readily converted to defined alkenyl boronic esters **6** and **8** employing procedures developed by Brown *et al.* (Scheme 1).[10] The key step was the cyclopropanation. We examined different Simmons-Smith protocols[11] as well as Pd(II)-catalyzed reactions of diazomethane[12] with alkenyl boronic esters and determined the influence on the diastereoselectivity and yield of the transformation.

We chose alkenyl boronic ester **9** - synthesized quantitatively by condensation of the corresponding heptenyl boronic acid and (+)-diisopropyl L-tartrate - as model compound for our investigation. Cyclopropanation furnished the relatively labile diastereoisomers **11a** and **11b** that we were never able to purify. However, ^{13}C nmr investigations allowed an estimation of the diastereomeric ratio. More precise data were gathered from glc analysis using chiral stationary phases after oxidation of the crude mixture to the enantiomeric cyclopropanols **12** and *ent*-**12** (Scheme 2). An excess of *ent*-**12** (determined by correlation with Imai's results)[6] was obtained when starting with **10**.



Scheme 1. *Reagents and Conditions*: i a) $HBBr_2$*DMS, CH_2Cl_2, 0 °C; b) 0 °C, pentane, 2.2 eq. R*OH (lit. 10a]). ii a) $HBBr_2$*DMS, CH_2Cl_2, 0 °C; b) NaOH, H_2O; c) Et_2O, 4Å ms, 2.2 eq. R*OH, reflux (lit. [10b]). iii a) n-BuLi, -78 °C, Et_2O; b) $B(O^iPr)_3$, Et_2O, -78 °C; c) anh. HCl in Et_2O, -78 °C to rt (lit. [10c]). iv a) H_2, Lindlar-cat., dioxane, pyridine, rt; b) H_2O; c) 2.2 eq. R*OH, Et_2O, 4Å ms, reflux (lit. [10d]).



Scheme 2

Imai, Mineta and Nishida reported very satisfactory diastereomeric excesses using the original Simmons-Smith procedure for the transformation **9** to **11a/11b**.[6] However, the yields were relatively low. This encouraged us to investigate the possibilities of the Furukawa method for the cyclopropanation, employing diethyl zinc and diiodo methane.[11a,b] We were rather disappointed that we could neither match the diastereomeric ratios nor improve the yields of the overall transformation (Table 1). The best selectivities we got (**11a**:**11b** in an 88:12 ratio; entry 1) were obtained after slow addition of diethyl zinc to a mixture of diiodo methane and the alkenyl boronic ester **9**. Changing the order of events or pre-forming the reagent did not improve the ratio. Finally, performing the cyclopropanation at lower temperatures gave higher yields of **12** (70%; entry 4).

We then started investigating the Carboni method.[12] The overall yields were always high (84-92%). However, the selectivity was strongly depending on the reaction conditions. For a given chiral auxiliary we examined four parameters possibly influencing the stereochemical result (Table 2): First, we observed that a higher starting concentration of **9** in diethyl ether was increasing the *ee* of cyclopropanol **12** (entries 5+6). This was obviously problematic since the addition of diazomethane was continiously diluting the reaction mixture, hence decreasing the *de* with time. The second parameter investigated was the

Table 1. [a] All reactions were performed in dichloromethane at 0 °C
Simmons-Smith-Reaction

Entry	*Conditions* [a]	**11a : 11b**	*ee* (**12**)	Yield (**12**)
1	diiodo methane (4 eq.) + (**9**), then diethyl zinc (2 eq.)	88 : 12	75%	56%
2	diethyl zinc (2 eq.) + (**9**), then diiodo methane (4 eq.)	80 : 20	60%	n.d.
3	diethyl zinc (2 eq.) + diiodo methane (4 eq.), then (**9**) (20 °C)	81 : 19	61%	46%
4	diethyl zinc (2 eq.) + diiodo methane (4 eq.), then (**9**) (-15 °C)	84 : 16	67%	70%

Table 2
Pd(II)-acetate catalyzed cyclopropanation with diazomethane

Parameter: Starting concentration of **9** in diethyl ether
Conditions:
-25 °C, 5 mol% Pd(II)-acetate, 25 ml diazomethane/mmol **9** in 15 min

Entry	ml diethyl ether/mmol **9**	**11a : 11b**	*ee* **12**
5	1	82 : 18	64
6	10	74 : 26	48

Parameter: Addition time of 25 ml diazomethane/mmol **9**
Conditions:
-30 °C, 3 mol% Pd(II)-acetate, 10 ml diethylether/mmol **9**

Entry	h/mmol **9**	**11a : 11b**	*ee* **12**
7	0.25	74 : 26	48
8	2	78 : 22	56
9	4	82 : 18	63

Parameter: Amount of catalyst
Conditions:
0 °C, 25 ml diazomethane/mmol **9** in 15 min, 1 ml diethylether/mmol **9**

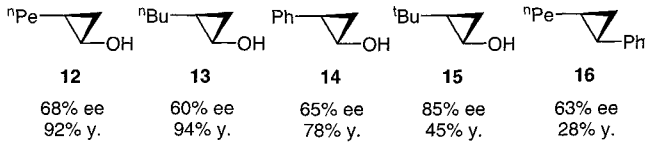
Entry	mol% Pd(II)-acetate	**11a : 11b**	*ee* **12**
10	0.5	83 : 17	66
11	5	83 : 17	65
12	15	82 : 18	63

Parameter: Temperature
Conditions:
25 ml diazomethane/mmol 9 in 15 min, 5mol% Pd(II)-acetate,
1 ml diethylether/mmol **9**

Entry	Temperature [°C]	**11a : 11b**	*ee* **12**
13	15	83 : 17	65
14	0	83 : 17	66
15	-15	84 : 16	68
16	-25	82 : 18	64
17	-78 (-40)	63 : 37	25
18	-36	63 : 37	25

time it took to add diazomethane to the reaction mixture. We normalized this process using 25 ml diazomethane in diethyl ether per mmol **9**. Entries 7-9 indicated that the slower the addition the better the *de* of the transformation. Note that this is only true, because we observed at low reaction temperatures and starting concentrations of **9** slow conversions to the products (compare with entry 15). The amount of Pd(II)-acetate used had no influence on the selectivity (entry 10-12). Whereas the ratio **11a:11b** was hardly influenced when keeping the reaction mixture between 15 °C and -25 °C, a dramatic loss of selectivity was observered when changing to lower temperatures (entry 13-18). In fact, at -78 °C no reaction occurred. At ~ -40 °C the first, slow development of nitrogen could be detected (entry 17). Leaving the reaction mixture at -36 °C gave the same result (entry 18).[13]

Having optimized the reaction conditions[14] we applied them to other examples (Figure 2) and got the corresponding cyclopropanols **13-15** in similar selectivities. The only exception was the synthesis of **15**. Although the enantiomeric excess was much higher (85%) than in all other cases the yield of the transformation was disappointing (45%). The first explanation, having a diastereoselective discrimination during the oxidation process, proved wrong, since the enantiomeric excess of **15** and the diastereomeric excess of the corresponding cyclopyl boronic esters were the same.



12 68% ee 92% y. **13** 60% ee 94% y. **14** 65% ee 78% y. **15** 85% ee 45% y. **16** 63% ee 28% y.

Figure 2

The synthesis of **12** was also achieved in a one-pot process starting from 1-heptin. However, the yield was only mediocre (27%). It was reasoned that both cyclopropanation (partial poisoning of the catalyst with dimethyl sulfide residues) and the oxidation (in diethyl ether instead of tetrahydrofuran) were rather sluggish.

In this paper we reported an optimized synthesis of cyclopropyl boronic esters starting from 1-alkynes elaborating the Carboni method. We are currently investigating the influence of other chiral auxiliaries on the selectivity and stability of these versatile intermediates. Other transformations, e.g. the Suzuki-coupling, that were possible with racemic cyclopropyl boronates,[8] but gave only unsatisfactory results in the coupling of **11a/11b** with phenyl iodide to furnish **16**, are the center of the ongoing research in our laboratories.

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(13) Note that the same selectivity (~ 25% *ee*) was obtained when adding Pd(II)-acetate to the reaction mixture after the addition of diazomethane under standard conditions.[14]

(14) *Typical experimental procedure:* 1-Heptenyl-boronic acid[10b] (425 mg, 3 mmol), 150 mg 4Å molecular sieves and (+)-diisopropyl L-tartrat (775 mg, 3.3 mmol) were refluxed in 6 ml dry diethyl ether under a nitrogen atmosphere. After 8 h the reaction mixture was filtered through a pad of celite and washed extensively with ether. The solvent was evaporated under reduced pressure to yield the crude product with the excess of diol [selected data for diisopropyl (*R,R*)-2-hept-1'-enyl-1,3,2-dioxaborolane-4,5-dicarboxylate **9**: δ_H (500 MHz; C_6D_6) 0.88 (t, *J* 7.2 Hz, 3H, 7'-H), 1.02 (d, *J* 6.3 Hz, 12H, 4 CH_3), 1.10-1.32 (m, 6H, 4'-H, 5'-H, 6'-H), 2.04 (m_c, 2H, 3'-H), 5.02 (hept., *J* 6.3 Hz, 2H, OC*H*(CH_3)$_2$), 5.12 (s, 2H, 4-H, 5-H), 5.82 (dt, *J* 17.9, 1.6 Hz, 1H, 1'-H), 7.12 (dt, *J* 17.9, 6.4 Hz, 1H, 2'-H); δ_C (125 MHz; C_6D_6) 14.05 (C-7'), 21.40 (4 CH_3), 22.78, 28.00, 31.60 (C-4', C-5', C-6'), 45.89 (C-3'), 69.55 (2* OCH(CH_3)$_2$), 78.45 (C-4, C-5), 116.75 (C-1'), 157.99 (C-2'), 169.19 (2 C=O); m/z [EI] (%): 340 [M^+] (2), 298 (39), 256 (95); HRMS: Found 340.2056 ($C_{17}H_{29}O_6B$ requires 340.2057)]. The crude product was dissolved in 3 ml dry diethyl ether, 6 mg Pd(II)-acetate were added and the mixture was cooled to -15 °C. Diazomethane in ether[15] (75 ml) was slowly added (45 minutes) *via* a precision-addition-funnel. The mixture was left at this temperature for 1 h, then allowed to warm-up to rt with continuous stirring. Filtration through a pad of celite and washing with ether furnished after evaporation of the solvent the crude cyclopropyl boronic ester. [Selected data for diisopropyl (1'*R*,2'*R*,4*R*,5*R*)-2-[2'-pentyl-cyclopropyl]-1,3,2-dioxaborolane-4,5-dicarboxylate **11a**: δ_H (500 MHz; C_6D_6) 0.03 (dt, *J* 9.2, 5.6 Hz, 1H, 1'-H), 0.54 (ddd, *J* 9.2, 5.6, 3.6 Hz, 1H, 3'-H_a), 0.96 (t, *J* 6.8 Hz, 3H, 5''-H), 1.01 (d, *J* 6.2 Hz, 6H, 2 CH_3), 1.02 (d, *J* 6.2 Hz, 6H, 2 CH_3), 1.04-1.50 (m, 10H, 3'-H_b, 2'-H, 1''-H, 2''-H, 3''-H, 4''-H), 4.99 (m, 2H, OC*H*(CH_3)$_2$), 5.01 (s, 2H, 4-H, 5-H); δ_C (125 MHz; C_6D_6) -0.72 (br, C-1'), 12.30 (C-3'), 14.28 (C-5''), 19.63 (C-2'), 21.41 (4 CH_3), 23.02, 29.61, 31.96 (C-2'', C-3'', C-4''), 35.38 (C-1''), 69.50 (2 OCH(CH_3)$_2$), 78.38 (C-4, C-5), 169.23 (2 C=O)]. Tetrahydrofuran (15 ml) and a mixture containing 30% H_2O_2 (0.5 ml) and 2N $KHCO_3$ (0.5 ml) was added and stirred 4 h at rt. Diethyl ether (25 ml) and water (15 ml) were added, the phases separated and the aqueous layer extracted twice with 10 ml diethyl ether. The combined organic layers were washed with saturated ammonium chloride solution, water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/diethyl ether 4:1) to furnish **12**/ent-**12** (354 mg, 2.76 mmol, 92%) as a colorless liquid (68% ee). Selected data for 2-pentyl-cyclopropan-1-ol **12**/ent-**12**: $[\alpha]_D^{21}$ = -16.5 (c = 2.16 in $CDCl_3$); δ_H (250 MHz; $CDCl_3$) 0.29 (bq, *J* ~6 Hz, 1H, 3-H_a), 0.67 (ddd, *J* 2.8, 5.5, 9.9 Hz, 3-H_b), 0.89 (t, 3H, 5'-H), 0.93 (m_c, 1H, 2-H), 1.01-1.69 (m, 8H, H-1', H-2', H-3', H-4'), 2.02 (br, 1H, OH), 3.19 (ddd, *J* 6.2, 2.8, 2.6 Hz, 1H, 1-H); δ_C (125 MHz) 14.06 (C-5'), 14.46 (C-3), 19.95 (C-2), 22.63 (C-4'), 28.64 (C-3'), 31.59, 31.60 (C-1', C-2'), 52.79 (C-1); ν_{max} [film] (cm^{-1}) 3600-3200 br (OH); m/z [EI] (%): 128 (2) [M^+], 110 (10), 95 (25), 66 (100), 54 (89); HRMS: Found 128.1202 ($C_8H_{16}O$ requires 128.1201).

(15) **Caution**: The generation and the handling with diazomethane requires special precautions: Lombardi, P. *Chem. Ind. (London)* Nov. 5, **1990**, 708; Moss, S. *ibid.* Feb. 21, **1994**, 122.