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# Regio- and stereoselective cyclopropanation of functionalised dienes. Novel methodology for the synthesis of vinyl- and divinyl-cyclopropanes

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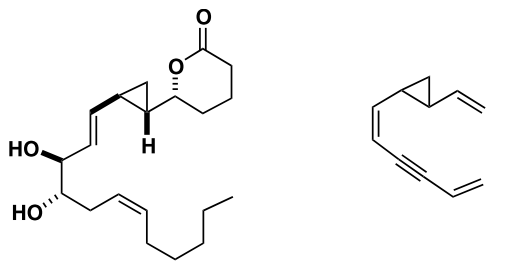
**Abstract**—Dienes, bearing an electron-withdrawing substituent at C-1, are cyclopropanated regio- and stereoselectively at the C–C double bond proximal to this electron-withdrawing group. The highest selectivity is observed in the case of dienylboronates. The cyclopropanation of these substrates affords almost exclusively the synthetically useful 1-boronato-2-vinyl-cyclopropanes. 

Numerous natural products contain, embedded in their often complex architectural framework, one or more vinylcyclopropane or divinylcyclopropane subunits (Fig. 1).

The unique physical and biological properties associated with this small ring system have stimulated enormous interest in its preparation, theoretical studies and subsequent transformations.[1] Whilst the vast majority of the reported synthetic methods allow the efficient construction of diversely substituted cyclopropanes, few reactions exist that produce directly, in a flexible and concise manner, functionalised vinylcyclopropanes.[2]




Constanolactone E **1**



Desmarestene **2**

**Figure 1.**

Our interest in the total synthesis of some of the above-mentioned natural products prompted us to investigate a novel route towards vinylcyclopropane and divinylcyclopropane residues based upon the direct, regio- and stereocontrolled cyclopropanation of substituted dienes **3** (Fig. 2).

Amongst the plethora of methods employed for the preparation of three-membered rings,[3] the $Pd(OAc)_2$/$CH_2N_2$-catalysed cyclopropanation of alkenes attracted our attention.[4] Whereas several publications describe the successful cyclopropanation of olefins bearing ketone,[5] oxazolidine[6] and boronate[7] substituents with this Pd(II) system, to the best of our knowledge, no report has yet appeared on the direct cyclopropanation of functionalised dienes.[8]

At the onset of our studies, several sorbate derivatives were prepared and treated with 1 equiv. of $CH_2N_2$ in the presence of 5 mol% of $Pd(OAc)_2$. The results are shown in Table 1.

As can be seen from Table 1, the regioselectivity of the palladium-catalysed cyclopropanation of **3** increases according to the electron-withdrawing ability of the dienyl substituent. Thus, reaction of the oxazolidinone derivative **3a** with $CH_2N_2/Pd(OAc)_2$ leads to a mixture of the proximal vinylcyclopropane **4a** and the distal vinylcyclopropane **5a** in a 2:1 ratio (entry 1). Ethyl sorbate **3b** also reacts smoothly, affording **4b** and **5b** in a slightly improved ratio of 4:1 (entry 2). Finally, ketone **3c** gives rise to the expected cyclopropanation

*Keywords*: dienylboronates; cyclopropanes; palladium; vinylcyclopropanes; Suzuki coupling.

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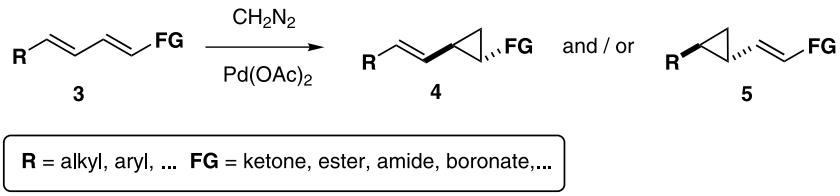



**Figure 2.**

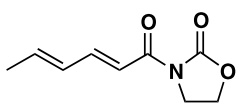
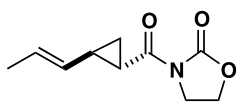
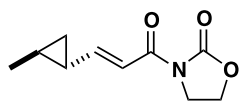
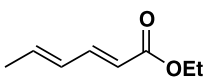
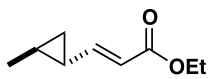
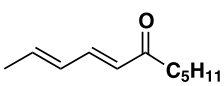
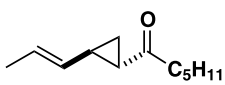
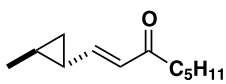
products **4c** and **5c** with a high selectivity (18:1) in favour of **4c** (entry 3). In all cases, variable amounts of bis-cyclopropanes were observed (Table 1, caption). It is noteworthy that only the *trans* cyclopropanes were obtained with virtually complete stereocontrol. The increasing preference for proximal cyclopropanation over distal addition as a function of the electron-withdrawing ability of the dienyl substituent, prompted us to investigate the reaction of the analogous dienylboronates.

The requisite starting dienes were readily prepared according to the procedure of Yates,[9] as shown in Fig. 3. Thus, Wittig olefination of aldehydes **6**, using the trimethylsilyl-protected ylid **7**, afforded, after desilylation, the corresponding (*E*)-enynes **8** in essentially quantitative yields. Hydroboration with catecholborane generated dienylboronates **9**, possessing almost exclusively the (*E*,*E*)-configuration. Finally, ligand exchange at the boron centre was readily accomplished by stirring **9** with pinacol or 1,3-propanediol, affording boronates **10** in 45–55% overall yields.[10]

With a variety of differently substituted dienylboronates **9** and **10** in hand, we next turned our attention to the crucial cyclopropanation reaction. Addition of $CH_2N_2$ to a cold solution of substrates **9**–**10**, containing 5 mol% of $Pd(OAc)_2$ resulted in their smooth conversion to the corresponding boron-containing vinylcyclopropanes. Some selected results are collected in Table 2.

As can be seen from Table 2, the palladium-catalysed cyclopropanation of **9**–**10** proceeds in all cases with good to excellent yields. The reaction tolerates a range of functionalities and protecting groups such as esters and silyl ethers (entries 3 and 4). It is noteworthy that, in all cases studied, cyclopropanation occurs with exquisite regio- and stereoselectivity on the C–C double bond proximal to the boron atom. Even more remarkable is the observation that simple alkenes are unaffected under these conditions; chemoselective cyclopropanation of the dienylboronate taking place even in the presence of highly reactive (*Z*)-olefins[11] (entry 5). Finally, the procedure tolerates a variety of substitution on the boron atom (entries 1, 6 and 7).

**Table 1.** Palladium-catalysed cyclopropanation of electron-deficient dienes **3**

| Entry | Substrate | Products (ratios)[a] | | |
|---|---|---|---|---|
| 1[b] |  |  | (2 : 1) |  |
| | **3a** | **4a** | | **5a** |
| 2[c] |  |  | (4 : 1) |  |
| | **3b** | **4b** | | **5b** |
| 3[d] |  |  | (18 : 1) |  |
| | **3c** | **4c** | | **5c** |

[a] All reactions were carried out using 1 equiv. of $CH_2N_2$ and 5 mol% of $Pd(OAc)_2$ in $Et_2O$ at 0°C. The ratios of isomers have been measured by 1H NMR spectroscopy and by capillary gas chromatography on the crude reaction mixtures.
[b] Conversion = 90%; the bis-cyclopropane is obtained in 20% yield (see text).
[c] Conversion = 93%; the bis-cyclopropane is formed in 10% yield.
[d] Conversion = 50%; the bis-cyclopropane is formed in 2% yield.

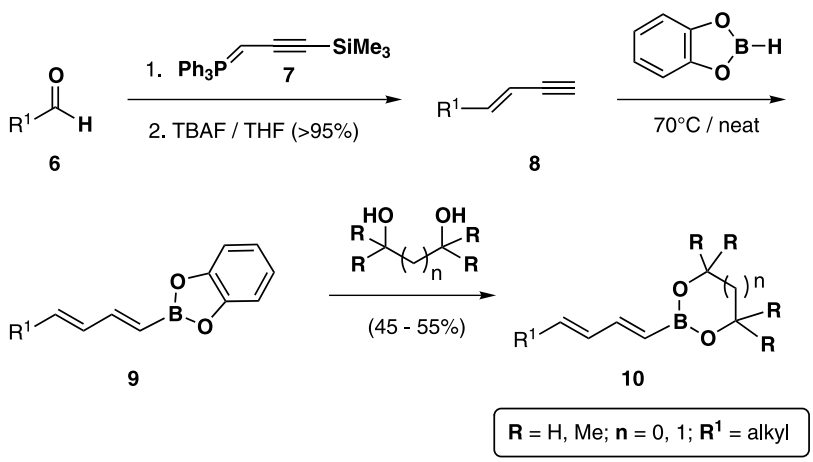
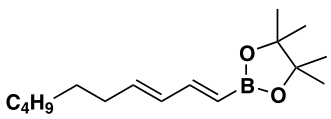
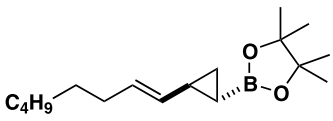
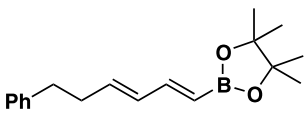
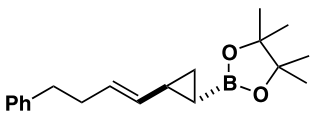
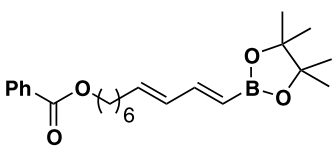
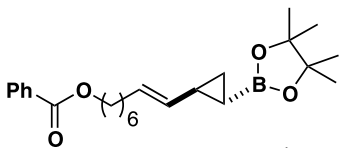
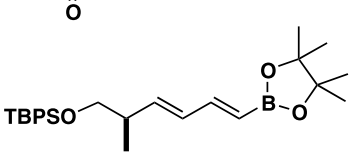
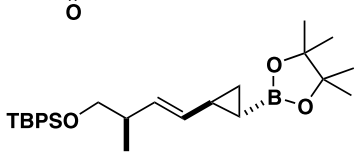
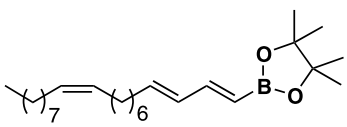
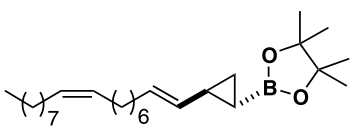
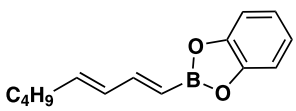
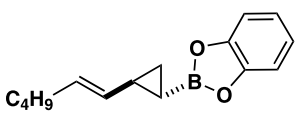
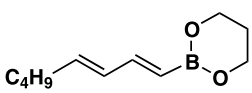
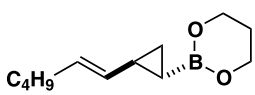



**Figure 3.**

**Table 2.** Palladium-catalysed cyclopropanation of dienylboronates

| Entry | Substrate | Product | Yields[a] |
|---|---|---|---|
| 1 |  |  | 70% |
| 2 |  |  | 66% |
| 3 |  |  | 65% |
| 4 |  |  | 61%[b] |
| 5 |  |  | 63% |
| 6 |  |  | 65%[c] |
| 7 |  |  | 66%[d] |

[a] All the reactions were conducted using 5 mol% of $Pd(OAc)_2$ and 1.5 equiv. of $CH_2N_2$ in $Et_2O$, at 0°C. Unless otherwise stated, all yields are for pure, isolated products. In all cases, only traces of the regioisomeric cyclopropane could be detected in the crude NMR spectrum. The conversions are quantitative but some decomposition occurs during the silica gel column chromatography.

[b] Obtained as a 1:1 mixture of diastereoisomers.

[c] This compound is unstable and hydrolyses rapidly, precluding complete purification.

[d] Isolated as the corresponding boronic acid after basic hydrolysis.

The powerful influence of the boron atom in directing proximal cyclopropanation with such high regiocontrol is difficult to reconcile by consideration of simple electronic effects. More work is required before any serious mechanistic rationale can be suggested. However, the results displayed in Tables 1 and 2 clearly reveal that the active species generated by the reaction of diazomethane with the palladium catalyst exhibits nucleophilic character and reacts faster with electron-deficient alkenes.[12]

In summary, we have developed a simple and efficient route to 1-boronato-2-vinylcyclopropanes from readily available dienylboronates.[13] The palladium-catalysed cyclopropanation is highly regio- and stereoselective, favouring almost exclusively the formation of the proximal cyclopropane. Furthermore, the procedure displays excellent tolerance towards a variety of functional groups. Current efforts are now being directed towards delineating the full scope of this novel methodology, uncovering an enantioselective version of this cyclopropanation reaction and applying our approach to the total synthesis of selected natural products. The results of these investigations will be reported in due course.

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## References

1. (a) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537; (b) Wong, H. N. C.; Hon, H. Y.; Tse, C. W.; Yip, Y. C. *Chem. Rev.* **1989**, *89*, 165.
2. Guerreiro, M. C.; Schuchardt, U. *Synth. Commun.* **1996**, *26*, 1793.
3. (a) Ziegler, F. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p. 899; (b) Reissig, H. U. In *The Chemistry of the Cyclopropyl Group*; Patai; Rappoport, Z., Eds.; Wiley: New York, 1987; Vol. 1, p. 417; (c) Salaün, J. In *The Chemistry of the Cyclopropyl Group*; Patai; Rappoport, Z., Eds.; Wiley: New York, 1987; Vol. 2, p. 849; (d) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, 2323 and references cited therein.
4. (a) Rodriguez-Garcia, C.; Ibarzo, J.; Alvarez-Larena, A.; Branchadell, V.; Oliva, A.; Ortuno, R. M. *Tetrahedron* **2001**, *57*, 1025; (b) Dzhemilev, U. M.; Dokichev, V. A.; Sultanov, S. Z.; Khursan, S. L.; Nefedov, O. M.; Tomilov, Y. V.; Kostitsyn, A. B. *Izv. Akad. Nauk. Ser. Khim.* **1992**, 2353; (c) Nefedov, O. M.; Tomilov, Y. V.; Kostitsyn, A. B.; Dzhemilev, U. M.; Dokichev, V. A. *Mendeleev Commun.* **1992**, 13; (d) For the recent use of metals other than Pd, see: Maas, G.; Seitz, J. *Tetrahedron Lett.* **2001**, *42*, 6137 and references cited therein.
5. (a) Mende, U.; Radüchel, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, *16*, 629; (b) Ortuno, R. M.; Ibarzo, J.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron Lett.* **1996**, *37*, 4059.
6. Abdallah, H.; Grée, R.; Carrié, R. *Tetrahedron Lett.* **1982**, *23*, 503.
7. (a) Fontani, P.; Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 4815; (b) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605; (c) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893; (d) Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977; (e) Pietruszka, J.; Witt, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293.
8. For interesting discussion on the direct cyclopropanation of dienes, see: (a) van Es, D. S.; Gret, N.; de Rijke, M.; van Eis, M. J.; de Kanter, F. J. J.; de Wolf, W. H.; Bickelhaupt, F.; Menzer, S.; Spek, A. L. *Tetrahedron* **2001**, *57*, 3557; (b) Cantrell, W. R., Jr.; Davies, H. M. L. *J. Org. Chem.* **1991**, *56*, 723; (c) Dzhemilev, U. M.; Dokichev, V. A.; Sultanov, S. Z.; Khusnutdinov, R. I.; Tomilov, Y. V.; Nefedov, O. M.; Tolstikov, G. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1989**, 1861.
9. Ahmed, M.; Barley, G. C.; Hearn, M. T. W.; Jones, E. R. H.; Thaller, V.; Yates, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1981.
10. In all cases, quantitative conversions are observed. However, purification by silica gel column chomatography induces significant decomposition of the dienylboronates, resulting in only modest yields of the pure products.
11. Suda, M. *Synthesis* **1981**, 714.
12. For some interesting discussions on the mechanism of these palladium-catalysed cyclopropanation reactions, see: (a) Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, P. E. *J. Org. Chem.* **1997**, *62*, 3375; (b) Rodriguez-Garcia, C.; Oliva, A.; Ortuno, R. M.; Branchadell, V. *J. Am. Chem. Soc.* **2001**, *123*, 6157.
13. **Typical experimental procedure**: Synthesis of 1-pinacoloboranyl-2-octenyl cyclopropane (Table 2, entry 1): *N*-Methyl-*N*-nitrosourea (460 mg, 4.44 mmol, 4 equiv.) was added portionwise to a stirred mixture of ether (2 mL) and 50% KOH (1 mL), cooled to 0°C. The ether layer rapidly became yellow and the reaction mixture was stirred at 0°C for another 30 min. The ether phase (containing the diazomethane) was separated and added dropwise to a cold (0°C) solution of the dienylboronate (293 mg, 1.11 mmol, 1 equiv.) and $Pd(OAc)_2$ (5.5 mg, 5 mol%) in ether. At the end of the addition, the solution was filtered through Celite and the solvent evaporated under reduced pressure. The dark residue was further purified by silica gel column chromatography, affording the title compound as a yellow oil (216 mg, 70%).
$^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.53 (1H, dt, $J^1=15.2$ Hz, $J^2=6.7$ Hz), 4.92 (1H, dd, $J^1=15.2$ Hz, $J^2=8.5$ Hz), 2.0–1.9 (2H, m), 1.56 (1H, m), 1.40–1.15 (20H, m), 0.95–0.85 (4H, m), 0.62 (1H, ddd, $J^1=9.7$ Hz, $J^2=5.3$ Hz, $J^3=3.5$ Hz), –0.11 (1H, ddd, $J^1=9.7$ Hz, $J^2=6.7$ Hz, $J^3=5.3$ Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 133.4, 128.7, 82.8, 32.4, 31.6, 29.5, 28.7, 24.6, 22.5, 20.2, 14.0, 12.2, 2.4. IR (neat) $\nu$: 1660, 1420, 1365, 1319, 1217, 1147 cm$^{-1}$. MS (CI/$CH_4$–$N_2O$): 279 ([M+H]$^+$). Anal. calcd for $C_{17}H_{31}BO_2$: C, 73.38; H, 11.23. Found: C, 73.45; H, 11.10.