Remarkable Stereocontrol in the Palladium-Catalysed Cyclopropanation of Vinyl- and Dienylboronates by Substituted Diazoalkanes

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Dedicated with deep respect to Professor Roger Sheldon on the occasion of his 60th birthday.

Abstract: Substituted diazoalkanes react smoothly, in the presence of catalytic amounts of $Pd(OAc)_2$, with a range of vinyl- and dienylboronates, affording in good to excellent yields, the corresponding trisubstituted cyclopropanes. The reaction is remarkably regio-, chemo-, and diastereoselective. The synthetic utility of this novel protocol is illustrated by the efficient assembly of the middle fragment of ambruticin.

Keywords: ambruticin; boronates; cyclopropanation; diastereoselectivity; diazoalkanes; palladium

Ambruticin **1**, isolated in the 1977 by scientists at Warner-Lambert,[1] is an interesting broad-spectrum antifungal antibiotic.[2] Besides its intriguing pharmacological activities, ambruticin possesses also a rather challenging architectural framework, embodying a unique trisubstituted divinylcyclopropane subunit. The unusual structure of **1** has aroused the interest of numerous research groups, resulting in the development of a wide range of elegant synthetic methodologies.[3] These endeavours culminated in 1990 with the first total synthesis of ambruticin by Kende and coworkers.[4] Whilst sporadic efforts continued to appear regularly, the fascination exerted by ambruticin slowly faded away, until recently when three different groups published almost simultaneously its total synthesis.[5]

Our own interest in ambruticin **1** led us to envision its disconnection into three fragments A, B, and C, as illustrated in Figure 1.[6]

Cleavage of the C_9-C_{10} and C_{16}-C_{17} bonds revealed a central subunit **2** that we envisaged to append onto the left-hand part A by a Suzuki cross-coupling procedure and to connect to the right-hand fragment C by a modified Julia protocol.[7] This middle portion **2** would originate from the stereocontrolled cyclopropanation of the dienylboronate precursor **3**.

At the onset of our work, we realised that this unique transformation, in order to be successful, had to fulfil a number of stringent criteria. Indeed, the cyclopropanation of **3** had to be highly regioselective, affording exclusively the proximal cyclopropane, completely stereoselective as regards to the (*E*)-double bond geometry, diastereoselective at the newly formed chiral centre bearing the methyl substituent, chemoselective (tolerant towards various protecting groups), and finally facial selective, giving rise solely to the enantiomer **2** and none of its optical antipode.

This large number of prerequisites prompted us to study initially the $Pd(OAc)_2$-catalysed cyclopropanation of model dienylboronates **4** in the presence of diazomethane.[8] We were gratified to find that **4** reacted smoothly with CH_2N_2, under the usual conditions, to

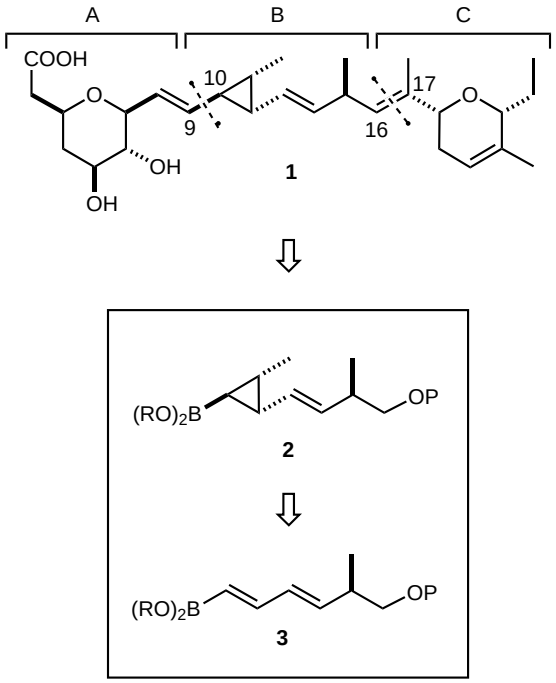

Figure 1. Antithetic analysis of ambruticin.

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afford almost exclusively the desired proximal cyclopropane **5.** In most cases, the regioselectivity proved to be essentially complete, with only traces of the distal cyclopropane being observed in some experiments. The reaction was also highly stereoselective, affording solely the *trans*-cyclopropane **5** from the (*E*)-dienylboronate precursor **4** (Figure 2).[9]

With these exciting results in hand, we next turned our attention to the use of diazoethane as the cyclopropanating agent and focused on the stereocontrol at the newly created chiral centre carrying the methyl substituent. Since, to the best of our knowledge, no palladium-catalysed cyclopropanation of unsaturated boronates, employing diazoalkanes other than diazomethane has been reported in the literature, we decided to investigate this transformation using initially simple vinylboronates (Figure 3).[10,11]

Thus, addition of a freshly prepared ethereal solution of CH_3CHN_2 to a mixture of vinylboronate **6** and $Pd(OAc)_2$ resulted in the smooth formation of **7** which was isolated in essentially quantitative yields as an 85:15 mixture of isomers. Careful ^1H NMR analysis clearly established that the major diastereoisomer possessed the relative stereochemistry indicated by structure **7** in which the methyl substituent is *syn* to the butyl sidechain and *anti* to the boron residue.

The unexpectedly high diastereoselectivity observed in this reaction prompted us to study its application to a range of functionalised vinylboronates. A selection of relevant examples is compiled in Table 1.

As can be seen from Table 1, the $Pd(OAc)_2$-catalysed cyclopropanation of substituted vinylboronates proceeds in all cases with good to excellent yields. The reaction is highly chemoselective, tolerating a variety of functions, including ester and silyl protecting groups. Whilst a remote ester substituent has no effect on the diastereoisomeric ratio (Entry 1, d.r. = 86:14), the nature of the silyloxy residue strongly influences the diastereoselectivity of the cyclopropanation reaction. Thus, whereas an allylic *t*-butyldimethylsilyloxy residue appears to act as an innocent bystander (Entry 2, d.r. = 83:17), the corresponding *t*-butyldiphenylsilyl ether leads to an increase in the diastereoisomeric ratio (Entry 3, d.r. = 93:7). The position of the silyloxy substituent with regards to the C-C double bond of the starting vinylboronate also impacts strongly on the diastereoselectivity of the reaction. For example, cyclopropanation of vinylboronates possessing an homoallylic *t*-butyldimethylsilyloxy substituent results in a much improved d.r. of 92:8 as compared to its allylic homologue (d.r. = 83:17; compare Entries 2 and 4). The combined, matched effects of position and nature of the silicon protecting group results in an exquisite diastereocontrol, affording the diastereoisomerically pure cyclopropane adduct (Entry 5). Whilst the intimate nature of the interactions governing such a high diastereocontrol is not yet fully understood, this novel methodology allows the rapid and stereoselective assembly of functionalised, trisubstituted cyclopropanes, of synthetic relevance.[12] Finally, the reaction is not limited to diazoethane and other diazo derivatives could be used with equal success. For example, $Pd(OAc)_2$-catalysed cyclopropanation of model substrate **6** using diazobutane also afforded smoothly the desired adduct, in essentially quantitative yield, and with a d.r. of 93:7 (Entry 6).

With these results in hand, attention was next devoted to the more complex problem of the cyclopropanation of dienylboronates. The starting substrates were readily prepared by hydroboration of the corresponding enynes, followed by ligand exchange, as described previously.[9] Some selected examples of the $Pd(OAc)_2$-catalysed cyclopropanation of dienylboronates with diazoethane are collected in Table 2.

As can be seen from Table 2, the cyclopropanation proceeds efficiently, affording the desired adducts in good yields. It is noteworthy that, in all cases, only the proximal cyclopropane is obtained implying that the extra methyl substituent does not alter the high regioselectivity previously observed using diazomethane. More remarkable is the uniformly high level of diastereocontrol exerted by the palladium catalyst on the newly created chiral centres, encompassing the one bearing the methyl residue (d.r. = 89:11 to 94:6). Finally, the reaction tolerates a range of functional groups, including a highly reactive (*Z*)-alkene (Entry 4).

The synthetic potential of this novel methodology was further illustrated by the efficient and concise assembly, in diastereomerically pure form, of the middle fragment **10** of ambruticin **1** (Figure 4).

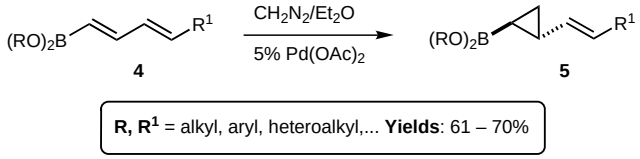


Figure 2. Palladium-catalysed cyclopropanation of dienylboronates.

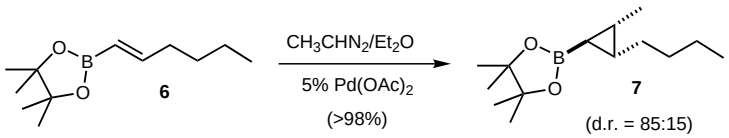
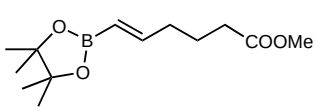
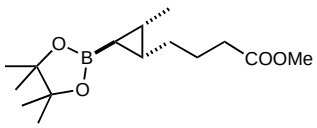
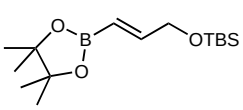
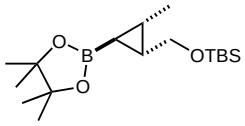
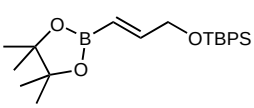
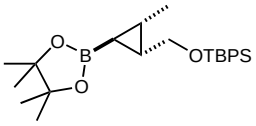
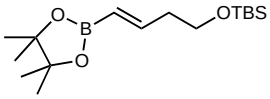
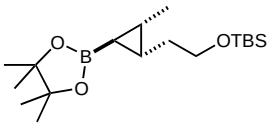
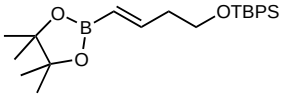
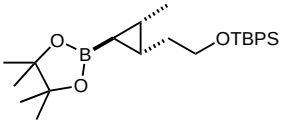
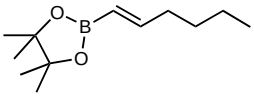
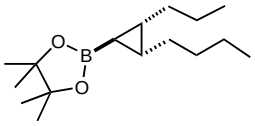


Figure 3. Palladium-catalysed cyclopropanation of vinylboronates.

Table 1. Diastereoselective cyclopropanation of vinylboronates.

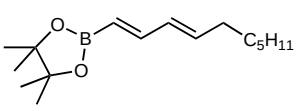
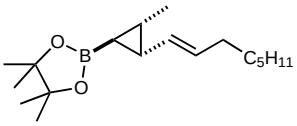
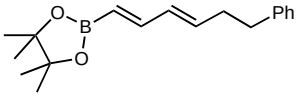
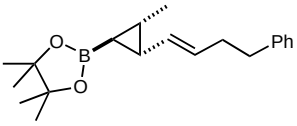
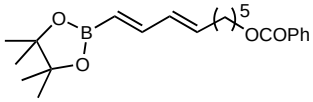
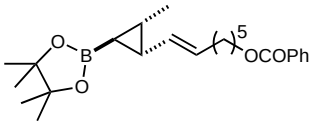
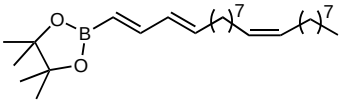
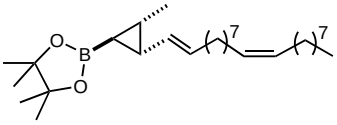
Entry	Substrate	Product	Yield[a]	d.r.
1			79%[b]	86:14
2			55%[c]	83:17
3			64%[d]	93:7
4			78%	92:8
5			76%	>99:1
6			99%[e]	93:7

[a] All yields are for pure, isolated product. Unless otherwise mentioned, all the reactions were carried out using 5 mol % $Pd(OAc)_2$ and 12 equivs of *N*-ethyl-*N*-nitrosourea.
[b] In this case, 24 equivs of *N*-ethyl-*N*-nitrosourea were employed.
[c] 20 mol % $Pd(OAc)_2$ were used.
[d] In this case, 20 mol % $Pd(OAc)_2$ and 24 equivs *N*-ethyl-*N*-nitrosourea were employed.
[e] *N*-Butyl-*N*-nitrosourea was employed in this case.

Thus, enyne **8**, readily available in optically pure form from β-hydroxybutyric acid, was chemo- and regioselectively hydroborated with catecholborane, generating the corresponding dienylboronate. Ligand exchange with the chiral auxiliary reported by Nakayama[13] and extensively employed by Pietruszka[11b,11e–g] afforded in 70% overall yield the desired substrate **9**. Cyclopropanation of **9**, using 5 mol % $Pd(OAc)_2$ in the presence of diazoethane, in ether, at 0 °C, smoothly produced the coveted proximal, trisubstituted cyclopropane **10** in 95% isolated yield. Most gratifyingly, both the facial selectivity (under the control of the chiral auxiliary) and the diastereoselectivity at the methyl-bearing centre proved to be almost perfect.[14]

In summary, we have shown for the first time that vinyl- and dienylboronates reacted smoothly with substituted diazoalkanes, in the presence of catalytic amounts of $Pd(OAc)_2$, to generate the corresponding trisubstituted, boron-containing, cyclopropane derivatives. The reaction tolerates a variety of functional groups and displays high chemo-, regio-, diastereo-, and facial selectivity. The power of this novel methodology has been illustrated by the efficient and concise synthesis of the diastereoisomerically pure middle fragment **10** of ambruticin. Further work is directed at exploring the full scope of this new protocol, completing the total synthesis of ambruticin **1** and applying this unique approach to the assembly of other relevant natural products.

Table 2. Diastereoselective cyclopropanation of dienylboronates.

Entry	Substrate	Product	Yield[a]	d.r.
1			68%	89:11
2			66%	94:6
3			65%	92:8
4			64%	92:8

[a] All yields are for pure, isolated product and all the reactions were carried out using 5 mol % $Pd(OAc)_2$ and 12 equivs of *N*-ethyl-*N*-nitrosourea.

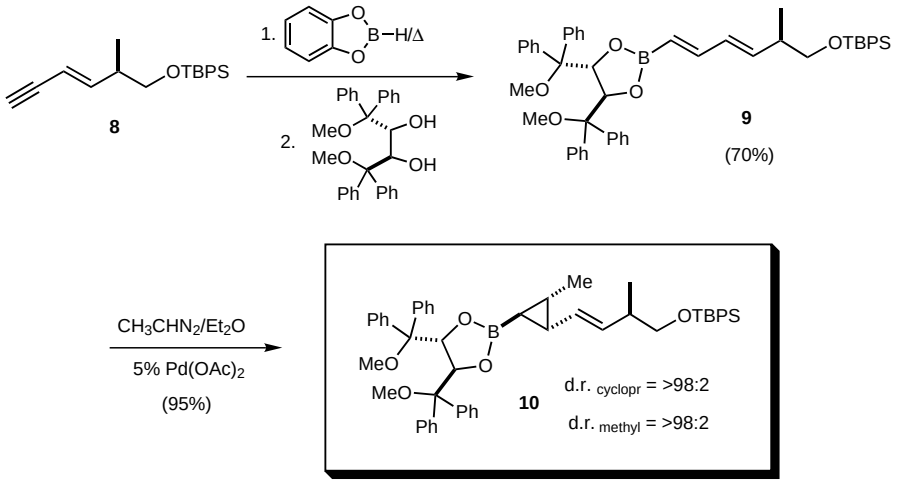


Figure 4. Diastereoselective Pd-catalysed cyclopropanation using diazoethane.

Experimental Section

Representative Procedure: Synthesis of *rac-tert*-Butyldiphenylsilyl-2-[(1*S*,2*S*, 3*R*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-1-ethyl Ether (Table 1, Entry 5)

To a suspension of *N*-ethyl-*N*-nitrosourea (322 mg, 2.75 mmol, 12 equivs) in anhydrous Et_2O (5 mL), at 0 °C, was added a 50% KOH solution (1 mL) within 30 seconds and the mixture was stirred for 15 minutes at 0 °C. The orange organic layer was transferred to a suspension of the vinylboronate (100 mg, 0.23 mmol) and $Pd(OAc)_2$ (5.2 mg, 0.023 mmol, 10 mol %) in ether (3 mL), at 0 °C, within 3 minutes and the mixture was stirred for 30 minutes at 0 °C. The solvent was removed under vacuum and the residue was purified by column chromatography (silica 5 g, petroleum ether-ether 10:1, 1% Et_3N) to give the title product as a colourless oil; yield: 81 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = -0.73$ (1H, dd, $J = 5.1$, 5.1 Hz), 1.01 – 1.28 (19H, m), 3.72 (2H, t, $J = 6.6$ Hz), 7.36 –

7.43 (6H, m), 7.67 – 7.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.87$, 16.67, 19.26, 19.97, 24.46, 24.76, 26.90, 32.00, 64.20, 82.68, 127.36, 129.36, 134.00, 135.47; high resolution MS: calcd. for $C_{29}H_{40}BO_3Si$: 463.2840; found: 463.2836.

Acknowledgements

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References and Notes

[1] S. M. Ringel, R. C. Greenough, S. Roemer, D. Connor, A. L. Gutt, B. Blair, G. Kanter, M. von Strandtmann, *J. Antibiot*. **1977**, *30*, 371.

[2] K. Gerth, P. Washausen, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot*. **1996**, *49*, 71.

[3] a) V. Michelet, K. Adley, B. Bulic, J.-P. Genêt, G. Dujardin, S. Rossignol, E. Brown, L. Toupet, *Eur. J. Org. Chem*. **1999**, 2885; b) H. Wakamatsu, N. Isono, M. Mori, *J. Org. Chem*. **1997**, *62*, 8917; c) L. Liu, W. A. Donaldson, *Synlett* **1996**, 103; d) T. Nagasawa, Y. Handa, Y. Onoguchi, S. Ohba, K. Suzuki, *Synlett* **1995**, 739; e) A. H. Davidson, N. Eggleton, I. H. Wallace, *J. Chem. Soc. Chem. Commun*. **1991**, 378. For an excellent review, see: D. R. Williams, J. J. Li, R. H. Hutchings, *Org. Prep. Proc. Int*. **2000**, *32*, 409.

[4] a) A. S. Kende, Y. Fujii, J. S. Mendoza, *J. Am. Chem. Soc*. **1990**, *112*, 9645; b) A. S. Kende, J. S. Mendoza, Y. Fujii, *Tetrahedron* **1993**, *49*, 8015.

[5] a) P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc*. **2001**, *123*, 10772; b) T. A. Kirkland, J. Colucci, L. S. Geraci, M. A. Marx, M. Schneider, D. E. Kaelin, S. F. Martin, *J. Am. Chem. Soc*. **2001**, *123*, 12432; c) E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim, W. S. Jang, *Angew. Chem. Int. Ed*. **2002**, *41*, 176.

[6] a) I. E. Markó, D. J. Bayston, *Synthesis* **1996**, 297; b) I. E. Markó, D. J. Bayston, *Tetrahedron* **1994**, *50*, 7141; c) I. E. Markó, D. J. Bayston, *Tetrahedron Lett*. **1993**, *34*, 6595.

[7] a) I. E. Markó, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares, S. Dolan, *Tetrahedron* **2001**, *57*, 2609; b) I. E. Markó, F. Murphy, S. Dolan, *Tetrahedron Lett*. **1996**, *37*, 2089.

[8] For an example of an interesting cyclopropanation using trimethylsilyldiazomethane – a safer surrogate to diazomethane – and palladium catalysts, see: T. Aoyama, Y. Iwamoto, S. Nishigaki, T. Shioiri, *Chem. Pharm. Bull*. **1989**, *37*, 253.

[9] I. E. Markó, T. Giard, S. Sumida, A.-E. Gies, *Tetrahedron Lett*. **2002**, *43*, 2317.

[10] For selected examples of cyclopropanation using $Pd(OAc)_2/CH_2N_2$, see: a) C. Rodriguez-Garcia, J. Ibarzo, A. Alvarez-Larena, V. Branchadell, A. Oliva, R. M. Ortuno, *Tetrahedron* **2001**, *57*, 1025; b) U. M. Dzhemilev, V. A. Dokichev, S. Z. Sultanov, S. L. Khursan, O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, *Izv. Akad. Nauk. Ser. Khim*. **1992**, 2353; c) O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, V. A. Dokichev, *Mendeleev Commun*. **1992**, 13; d) U. Mende, B. Radüchel, W. Skuballa, H. Vorbrüggen, *Tetrahedron Lett*. **1975**, *16*, 629; e) R. M. Ortuno, J. Ibarzo, A. Alvarez-Larena, J. F. Piniella, *Tetrahedron Lett*. **1996**, *37*, 4059; f) H. Abdallah, R. Grée, R. Carrié, *Tetrahedron Lett*. **1982**, *23*, 503; g) P. Fontani, B. Carboni, M. Vaultier, R. Carrié, *Tetrahedron Lett*. **1989**, *30*, 4815; h) P. Fontani, B. Carboni, M. Vaultier, G. Maas, *Synthesis* **1991**, 605; i) J. P. Hildebrand, S. P. Marsden, *Synlett* **1996**, 893.

[11] For selected references on the asymmetric cyclopropanation of vinylboronates, see: a) T. Imai, H. Mineta, S. Nishida, *J. Org. Chem*. **1990**, *55*, 4986; b) J. E. A. Luithle, J. Pietruszka, *Liebigs Ann./Recueil* **1997**, 2297; c) A. B. Charrette, R. P. De Freitas-Gil, *Tetrahedron Lett*. **1997**, *38*, 2809; d) S.-M. Zhou, M.-Z; Deng, L.-J. Xia, M.-H. Tang, *Angew. Chem. Int. Ed.* **1998**, *37*, 2845; e) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **1999**, *64*, 8287; f) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem*. **2000**, *65*, 9194; g) J. Pietruszka, A. Witt, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4293.

[12] For some interesting discussions on the mechanism of these palladium-catalysed cyclopropanation reactions, see: a) S. E. Denmark, R. A. Stavenger, A. M. Faucher, P. E. Edwards, *J. Org. Chem*. **1997**, *62*, 3375; b) C. Rodriguez-Garcia, A. Oliva, R. M. Ortuno, V. Branchadell, *J. Am. Chem. Soc*. **2001**, *123*, 6157.

[13] K. Nakayama, J. D. Rainier, *Tetrahedron* **1990**, *46*, 4165.

[14] The relative stereochemistry was deduced from the value of the coupling constants of the cyclopropane protons. In all cases, the coupling constants for H-1 for the major diastereoisomer are in the range of 5.0 to 6.0 Hz whilst they comprised between 8.4 to 9.9 Hz for the minor diastereoisomer. The absolute stereochemistry was inferred from the model proposed by Pietruszka (Ref.[11e]). Chemical correlation to establish unambiguously the absolute stereochemistry of **10** is currently underway.