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4-*exo-dig* Cyclocarbopalladation: A Straightforward Synthesis of Cyclobutanediols from Acyclic γ-Bromopropargylic Diols under Microwave Irradiation Conditions

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In memory of our friend and colleague Dr Philippe Klotz

Keywords: Cyclocarbopalladation / 4-*exo-dig* cyclization / Microwaves / Bis(alkylidene)cyclobutane

Treatment of acyclic γ-bromopropargylic diols with tributylstannylated alkynes under palladium catalysis and microwave irradiation conditions gives high yields of the bis(alkylidene)cyclobutanediol derivatives and cyclobutenediols through an efficient 4-*exo-dig* cyclocarbopalladation. The cyclization is general with a wide variety of alkyne derivatives and gives access to new cyclobutane ring systems bearing one exocyclic double bond and one eneyne substituent as well as bicyclic dienes sharing a common double bond that may be of interest for further elaborations of complex molecules.

Introduction

The discovery of new reactions that allow the construction of new, complex or exotic molecules, particularly through the use of transition metal catalysis, has been widely explored in recent years.[1] Notably, palladium,[2] platinum,[3] gold[4] and rhodium[5] have recently been applied in several ring-expansion, tandem, cascade or domino processes for the construction of new polycyclic systems and the formation of new C–C or C–X bonds (X = O, N, S) in single operations. In this context we have recently discovered a new cyclization reaction based on a 4-*exo-dig* cyclocarbopalladation[6] that gives strained polycyclic derivatives (**4**–**9**, Scheme 1), in some cases possessing *anti*-Bredt double bonds shared by three cycles, as shown in compounds **4** and **5** (Scheme 1).

Eventually, access to the tricyclic core structures **8** and **9** of the ophiobolin and aleurodiscal natural products by this methodology was shown to be possible,[7] the reaction originally being carried out with compounds of type **1**–**3** with $Pd(PPh_3)_4$ catalysis in benzene or toluene at 85–90 °C in the presence of a vinyl- or alkynylstannane reagent. The potential synthetic utility of this reaction prompted us to study its scope and limitation.

To this end, and to broaden the usefulness of the 4-*exo-dig* cyclocarbopalladation, we firstly decided to use acyclic vinylic bromides of type **10** (Scheme 2) and secondly to explore new reaction conditions involving the use of microwave irradiation as a source of molecular activation of the catalytic process. Here we present the synthesis of highly substituted cyclobutanedienynes **11**, in high yields ranging from 71–86%. Bis(alkylidene)cyclobutane derivatives have been known for some time[8] and have recently been obtained in good yields through organometallic-mediated synthesis, with use of copper or palladium activation.[9]

In the presence of heteroaromatic tin derivatives, it is also possible to obtain new heteroaromatic substrates of type **12**. If a vinylic stannylated reagent is used in place of an alkynylic one, bicyclic systems of type **13** can be obtained in good to moderate yields after a 6π-electrocylization reaction (Scheme 2). We have already previously reported several examples of this kind of reaction affording exotic polycycles.[6b] The starting γ-bromopropargylic diol **16** (Scheme 3) was easily accessible from the *trans*-cinnamaldehyde (**14**) in a two-step sequence.

Compound **14** was first subjected to a bromination/debromination step by standard procedures.[10] The product **15** was obtained in 84% yield as a mixture of *trans* and *cis* stereoisomers in a 1:1 ratio and this mixture was easily separated by chromatography on silica gel. For the first experiments, diol **15***trans* was selected as the starting material in order to minimize the stereoelectronic interactions between the phenyl group on the double bond and the new incorporated triple bond or double bond that might – in **15***cis*, for example – prevent the efficiency of the final coupling and eventually the 6π-electrocyclization process. The

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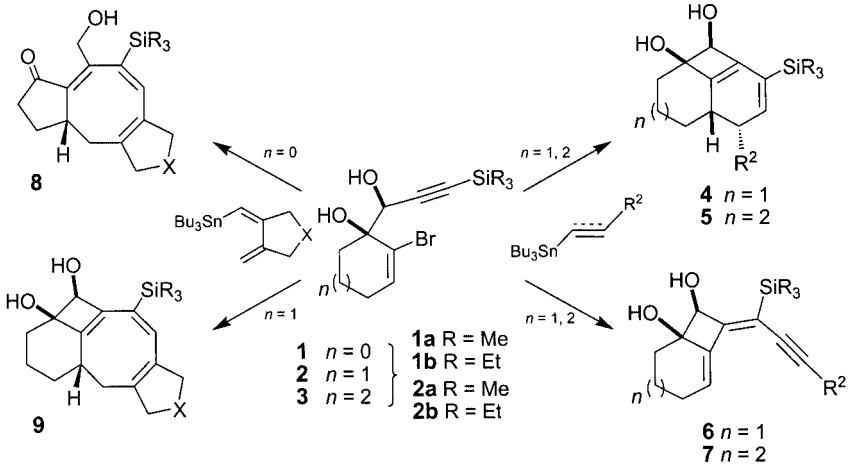
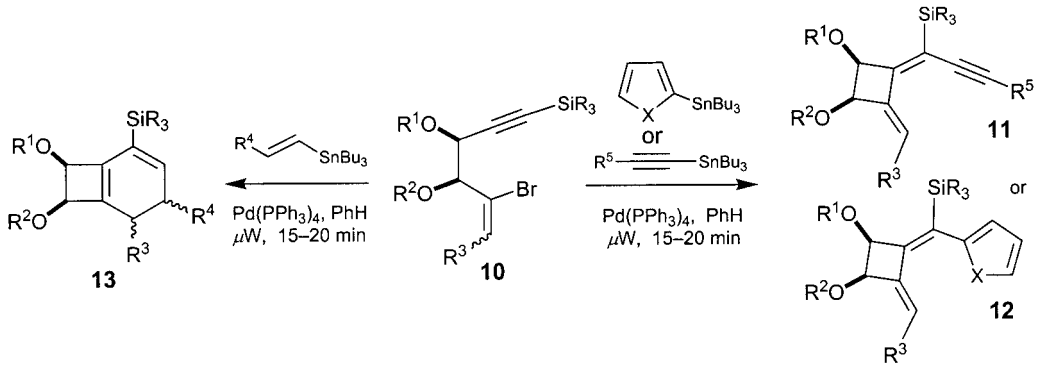


Scheme 1. 4-*exo-dig* cyclocarbopalladation – routes to polycyclic structures.

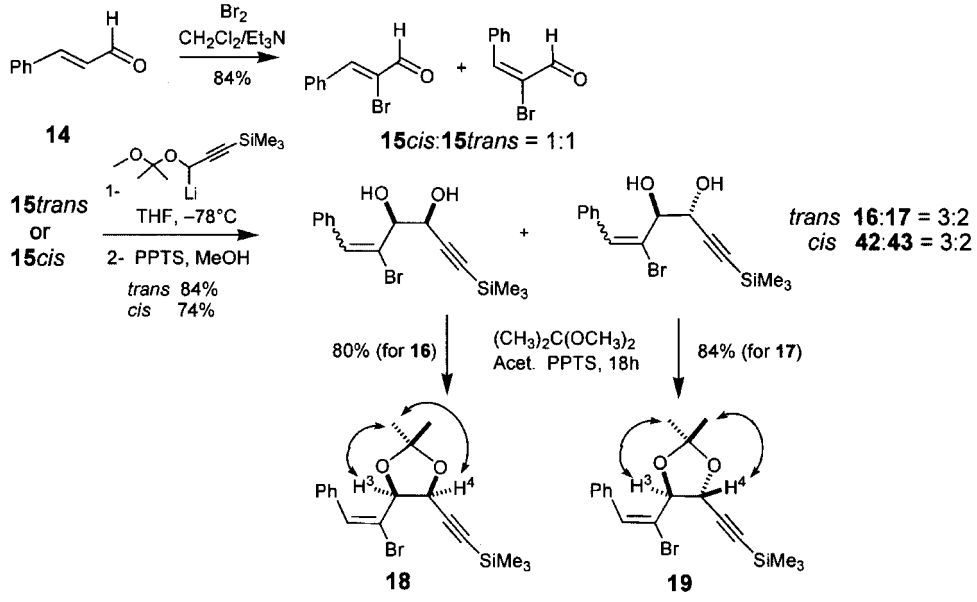


Scheme 2. Reactivity of acyclic γ-bromopropargylic diols.

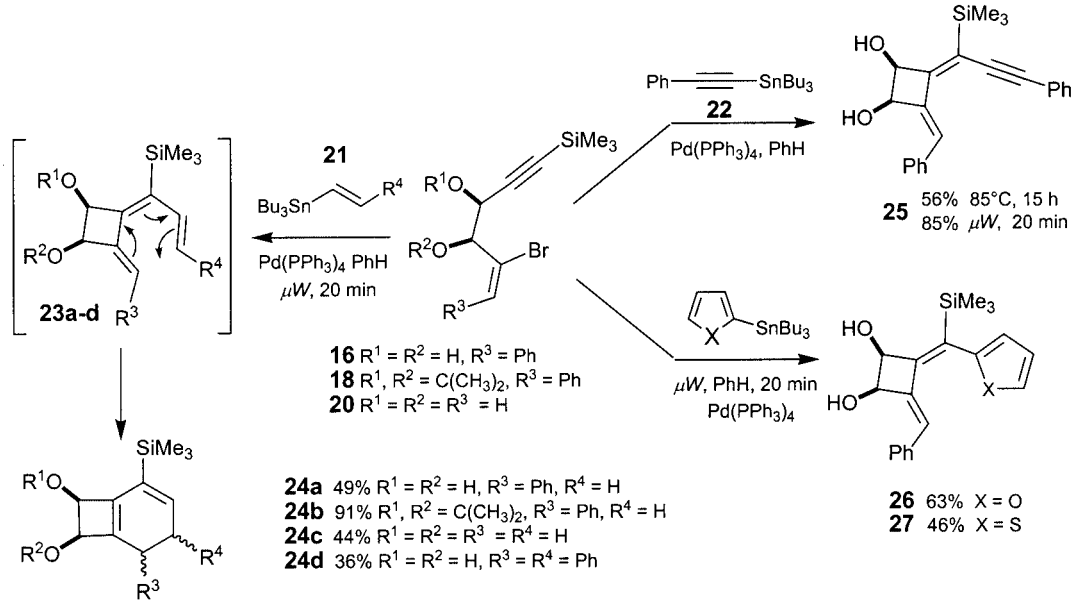
anti diol **16** and the *syn* **17** diol were isolated in 84% total yield and in a 3:2 ratio through the addition of the lithium salt of a suitably protected propargylic alcohol to the bromoaldehyde **15***trans*, followed by deprotection and chromatographic separation.[11]

The stereochemistries of the two diols were unambiguously determined by NMR 2D-NOESY experiments on the two dioxolane derivatives **18** and **19**. In **18**, strong correlations were observed between the protons H^3 and H^4 and just one methyl, but in **19** each methyl correlated with only one proton (H^3 or H^4; Scheme 3). From our previous results obtained with 4-*exo-dig* cyclocarbopalladations of cyclic propargylic diols[6b] we first intended to study only the reactivity of isomer **16**, which was expected to give higher yields of the cyclized products. In order to avoid decomposition of these highly sensitive compounds we turned our attention to the use of microwave irradiation, which would be expected to give better results in a shorter reaction time. Many examples describing the enhancement of yields, improvements in the efficiency in the course of the reaction, the absence of side products and short reaction times are available in the literature.[12] In a first set of experiments, treatment of **16**, **18** and **20** with vinyltributylstannane **21**[13] in the presence of palladium catalysis [10 mol-% Pd-$(PPh_3)_4$] in benzene afforded the cyclocarbopalladation products **23a**–**d**, which immediately cyclized through a 6π-electrocyclization process to give bicyclic products **24a**–**d**. It is important to note that under these conditions the protection of the diol as a dioxolane gave **24b** in a very high yield (91%) as a mixture of two diastereomers in a 1:1 ratio, whilst if unprotected diol **16** was used, **24a** (49%) was isolated as a single diastereomer, the phenyl group *anti* to the two OH groups. The sensitive role of the protection is not yet well understood and will be further studied.

In a second set of experiments, diol **16** was treated under "classical conditions" with 1.3 equiv. of (tributylstannyl)-phenylacetylene[14] (**22**) and $Pd(PPh_3)_4$ (10 mol-%) in benzene at 85 °C for 15 h. The stable cyclobutanediol **25** was isolated after silica gel chromatography in 56% yield. When **16** was then subjected to the same reaction conditions but under microwave irradiation for 20 min, **25** was isolated in 85% yield (Scheme 4). Similarly, treatment of **16** in the presence of the aromatic heterocycles derived from thiophene and furan produced **26** and **27** in 63 and 46% yields, respectively (Scheme 4). These optimized conditions were selected for the formation of other products containing the dienyne moiety; the investigation of additional substrates is summarized in Table 1. In all cases the reaction was run at 130 °C



Scheme 3. The preparation of acyclic γ-bromopropargylic diols.

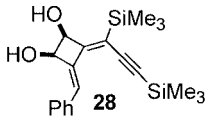
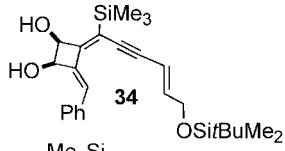
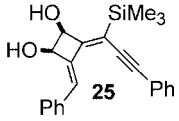
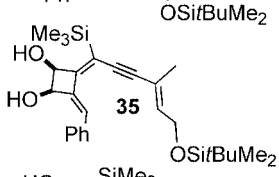
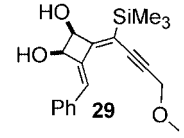
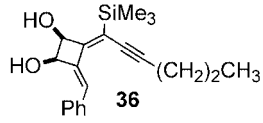
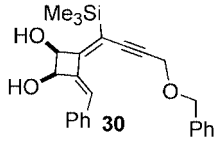
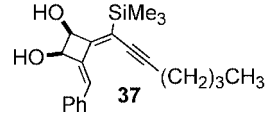
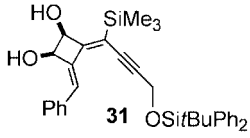
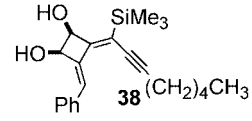
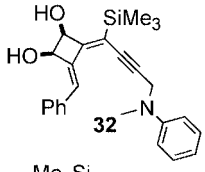
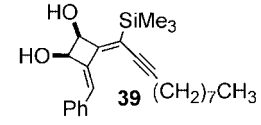
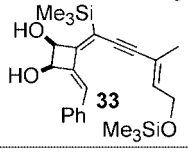
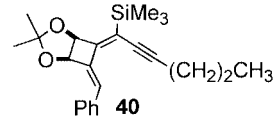


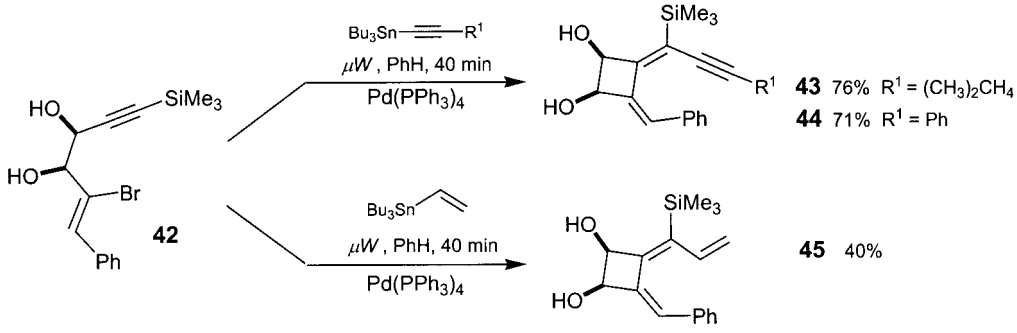
Scheme 4. First results in the 4-*exo-dig* cyclocarbopalladation.

over 20 min under initial microwave irradiation at 300 W, in a degassed solution of benzene in the presence of 1.3 equiv. of the stannylated reagent and $Pd(PPh_3)_4$ (10 mol-%).[15] Usually the solution turned dark brown after irradiation and the product was isolated by standard procedures and chromatographic purification on silica gel. The 4-*exo-dig* cyclocarbopalladation is effective with a large variety of functionalities on the triple bond, and yields of the corresponding dienynecyclobutanediols were between 71 and 86% (Entries 1–14, **25**, **28**–**40**). If **42** was used in place of **16** as a starting diol, the 4-*exo-dig* reaction was still effective (Scheme 3), with the incorporation of triple bonds giving **43** in 76% yield and **44** in 71% yield (Scheme 5). The 6π-electrocyclization was not observed when the tributylvinylstannane was coupled, **45** being isolated as the sole product in a modest yield of 40% (Scheme 5).

In summary, we have developed a new application of the 4-*exo-dig* cyclocarbopalladation of acyclic γ-bromopropargylic diols that allows an efficient preparation of new derivatives of cyclobutanediols in good yields. The efficiency of the reaction is greatly improved by the use of brief microwave irradiation at 130 °C. If the reaction was conducted in the presence of a vinyltributylstannane reagent a further 6π-electrocyclization occurred, providing new bicyclic systems. All the new products constitute new building blocks for the elaboration of substituted polycyclic molecules. Further

Table 1. 4-*exo-dig* Cyclocarbopalladation of acyclic propargylic diols with some alkynestannanes.

Entry	Cycloadduct	Yield [%]	Entry	Cycloadduct	Yield [%]
1	 **28**	80	8	 **34**	75
2	 **25**	85	9	 **35**	71
3	 **29**	84	10	 **36**	86
4	 **30**	72	11	 **37**	85
5	 **31**	80	12	 **38**	80
6	 **32**	79	13	 **39**	80
7	 **33**	77	14	 **40**	79



Scheme 5. Reactivity of the *cis*-γ-bromopropargylic diol.

studies will focus on the use of this methodology in this direction.

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[15] **General Procedure. 4-*exo-dig* Cyclocarbopalladation under Microwave Irradiation (Biotage System Initiator):** The reaction was carried out in a special BIOTAGE flask, under argon atmosphere. To a solution of the diol (1 equiv.) in dried benzene (2 mL), was added $Pd(PPh_3)_4$ (0.1 equiv.) and followed by the stannylated reagent (1.3 equiv.). The mixture was purged 20 min with argon and heated at 130 °C under microwave irradiation. The reaction was followed by TLC. After the reaction time, the mixture was cooled, diluted with Et_2O (10 mL), treated with active charcoal, filtrated over celite, and concentrated to dryness. The reaction mixture was purified by flash chromatography (in the majority of the cases two chromatography are necessary).

(1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[3-phenyl-1-(trimethylsilyl)prop-2-ynylidene]cyclobutane-1,2-diol (25): This compound was prepared according to the General Procedure on 0.295 mmol scale and with a reaction time of 20 min. Purification by flash chromatography with elution with Et_2O/heptanes (20:80) afforded the product (90 mg, 85%) as a yellow solid. R_f = 0.36 (Et_2O/heptanes, 30:70). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 1.5 Hz, 1 H, Ar*H*), 7.63 (d, J = 7.1 Hz, 2 H, Ar*H*), 7.48 (d, J = 1.5 Hz, 1 H, Ar*H*), 7.45 (d, J = 1.5 Hz, 1 H, Ar*H*), 7.38–7.31 (m, 6 H, Ar*H*, Ph–C*H*), 4.99 (t, J = 5.6 Hz, 1 H, HO–C*H*–CH–OH), 4.81 (t, J = 6 Hz, 1 H, HO–CH–C*H*–OH), 3.74 (br. s, 1 H, O*H*), 3.61 (br. s, 1 H, O*H*), 0.32 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 142.8, 135.8, 131.2, 129.7, 129.5, 128.6, 128.5, 128.3, 128.1, 124.2, 121.0, 103.4, 91.9, 72.4, 71.3, –1.0 ($SiMe_3$) ppm. IR (FITR, film): $\tilde{\nu}$ = 3400 (br), 2118, 1646, 1485, 1249, 1047, 976, 844, 756 cm^{-1}. HRMS (ESI, positive ion 180 eV): calcd. for $(C_{23}H_{24}O_2SiNa)^+$: 383.1441; found 383.1502.

(7*R*,8*S*)-5-Phenyl-2-(trimethylsilyl)bicyclo[4.2.0]octa-1(6),2-diene-7,8-diol (24a): This compound was prepared by the general procedure on 0.295 mmol scale, with use of 0.383 mmol of stannane and a reaction time of 30 min. Purification by flash chromatography with elution with AcOEt/heptanes (20:80) afforded the product (65 mg, 49%) as a white solid. R_f = 0.36 (Et_2O/heptanes, 30:70). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 3 H, Ar*H*), 7.17–7.12 (m, 2 H, Ar*H*, Ph–C*H*),

6.10 (t, J = 4.9 Hz, 1 H, Ar*H*), 4.85 (d, J = 3 Hz, 1 H, HO–C*H*–CH–OH), 4.73 (d, J = 3 Hz, 1 H, HO–CH–C*H*–OH), 3.70 (dd, J = 11 Hz, J = 5 Hz, 1 H, C*H*–CH_2), 2.94–2.45 (m, 4 H, CH_2, O*H*), 0.18 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.2, 147.2, 137.7, 132.1, 128.7, 127.2, 126.6, 73.0, 72.9, 36.1, 35.4, –1.5 ($SiMe_3$) ppm. IR (FITR, film): $\tilde{\nu}$ = 3410 (br), 2924, 2845, 1652, 1490, 1448, 1250, 1107, 1062, 893, 749 cm^{-1}. HRMS (ESI, positive ion 180 eV): calcd. for $(C_{17}H_{22}O_2SiNa)^+$: 309.1287; found 309.1253.

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