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Cyclocarbopalladation: 5-Exo-dig Cyclization versus Direct Stille Cross-Coupling Reaction. The Influence of the α,β-Propargylic Substitution

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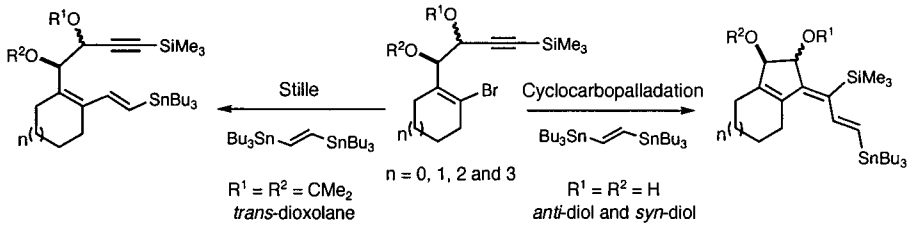
ABSTRACT



Several bicyclic compounds bearing a 1,2-cyclopentanediol have been prepared from various *anti*- or *syn*-γ-bromopropargylic diols and *cis*-dioxolanes under palladium(0) catalysis. The reaction proceeds through a 5-exo-dig cyclocarbopalladation. When the corresponding *trans*-dioxolanes are used, the only products isolated are obtained from a direct Stille cross-coupling reaction.

The cyclocarbopalladation process was described for the first time in 1988 by Grigg[1] shortly followed by Negishi.[2] This reaction afforded stereodefined exocyclic alkenes. 5-, 6-, or 7-exo-dig cyclocarbopalladations have been performed with success. The process can be ended by a terminating cross-coupling reaction either with a hydride source, an alkene, CO, or various organometallic reagents (aluminum, zirconium, boron, zinc, or tin derivatives). The cyclizations give acceptable yields when the substrate bearing the triple bond is an aromatic, but in most of the cases, the propargylic or homopropargylic positions are unsubstituted. The corresponding reaction has not been extensively investigated with acyclic[3] or cycloalkyl[4] substrates. Our initial studies recently focused on a rare 4-exo-dig cyclocarbopalladation of *anti*- and *syn*-propargylic-1,2-diols through Pd(0) catalysis.[5] Depending on the starting substrate, the only isolated product resulted from the cyclocarbopalladation coupling and not from a direct Stille cross-coupling reaction. We report herein an efficient 5-exo-dig cyclocarbopalladation of several propargylic diols leading to [3.0.3], [4.0.3], [5.0.3], and [6.0.3] substituted bicyclic diols (Figure 1). These carbon substructures are present in many natural products and can be used as starting materials for the design of more sophisticated complex polycyclic compounds.

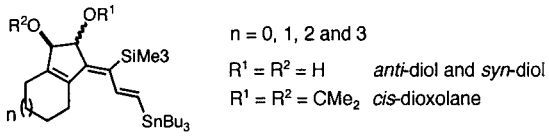


Figure 1.

(1) (a) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325. (b) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 5565.

(2) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

(3) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. *Tetrahedron Lett.* **1990**, *31*, 4393.

(4) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P. *Tetrahedron Lett.* **1989**, *30*, 1135.

(5) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845.

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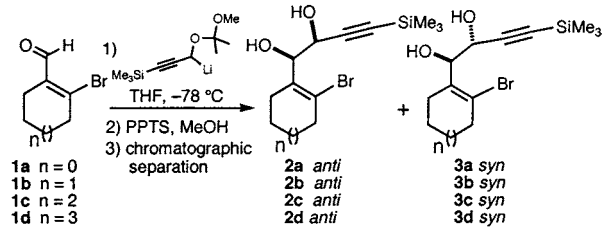
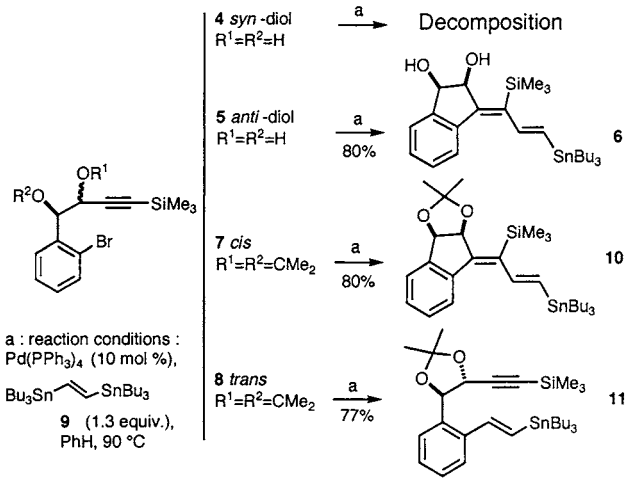
First, the starting materials, diols anti **2a**−**d** and syn **3a**−**d**, were prepared in good yields by addition of a properly protected metalated propargylic alcohol on bromoaldehydes **1a**−**d** (Scheme 1) followed by deprotection and chromato-

Scheme 1



graphic separation of the two anti and syn diastereomers.[6] The anti relative stereochemistry of the diol was established by ^{1}H-NOESY experiments on **24**, a derivative of **2b**.[7] The initial studies were performed on **7** and **8**, and two aromatic analogues of **2b** and **3b** were prepared following an identical route (Scheme 2) as described in a previous paper.[6]

Scheme 2



The reaction proceeds at 90 °C in benzene in the presence of a catalytic amount of $Pd(PPh_3)_4$ (10 mol %) and the bis-(tributylstannyl)ethylene **9**.[8] When dioxolane **7** was heated under these conditions, diene **10** was isolated in 80% yield. The same conditions applied on the trans stereomer **8** only gave **11** through the direct Stille cross-coupling reaction in a comparable yield (77%). The difference in reactivity between these two compounds is explained by the nonfeasible formation of a trans-fused bicyclo[3.0.3]dioxolane that prevented the cyclocarbopalladation process on **8**. After the initial oxidative insertion of palladium(0) in the carbon−bromine bond, the protection of diol as a cis-fused bicyclo-[3.0.3]dioxolane **7** brought the alkyne function and the palladated site closer together thereby favoring the cyclization process. The high yield observed for the formation of **6** (80%, $R_1 = R_2 = H$) could be explained by the presence in the anti diol **5** of a strong hydrogen bond which, closely related to **7**, settles the triple bond in close proximity to the metallic reactive center resulting in a clean carbopalladation of the alkyne moiety. This intramolecular pallado-assisted carbocyclization is kinetically favored and surely much faster than an intermolecular addition of the vinylstannane moiety.

Surprisingly, the unprotected syn diol **4** only gave decomposition of the reaction mixture when subjected to the same conditions. The results of the reaction of several propargylic diols are summarized in Table 1. The reaction time varied from 14 to 27 h, depending on the starting substrate, and was stopped when no evolution of the reaction was observed by TLC. Without any aqueous workup, the crude reaction mixture was evaporated in vacuum and directly chromatographed on silica gel pretreated by a solution of 5% Et_3N in diethyl ether to avoid the protodestannation of the product. In some cases (entry **1**, **2**, and **5**) this reaction also produced a small amount of the other isomer at the tetrasubstituted exocyclic double bond. The ratio of the two isomers seems to be dependent on the reaction time. The origin of this isomerization is not clear but could be explained by a Pd-assisted isomerization. The stereochemistry of the exocyclic diene chain was clearly established by NOESY experiments on compounds **14a**, **14b** (entry **1**, Table 1), and **26** (entry **1**, Table 2). For example, strong correlations were obtained between protons H^2 and the trimethylsilane group as well as between protons H^4 and H^8 in compound **26** (Figure 2).

Better yields and cleaner reactions were usually obtained with the anti diols when compared with the syn diols (entry **1** versus **5**, **2** versus **6**, **3** versus **7**). The eight-membered-ring starting diol **2d** (entry **4**, Table 1) gave only a 27% yield in the anti group and a complete decomposition of **3d** in the syn group. This low yield could be due to unfavorable entropic factors, which disfavored the formation of a bicyclo-[6.0.3] system.

When the OH group was not present at the benzylic position in **12**, the cyclization still proceeded to give **21** in 61% yield (entry **9**). Besides, a 6-exo-dig process afforded **22** as a single stereoisomer as determined by ^{1}H and ^{13}C NMR analysis, but only in 30% yield (entry **10**). The relative stereochemistry in **22** has not been established because of the nonsignificant coupling constant observed between the two vicinal hydrogens α to the hydroxyl groups, which can be cis or trans.

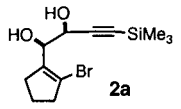
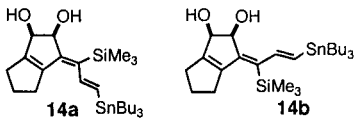
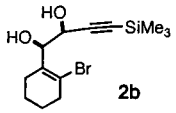
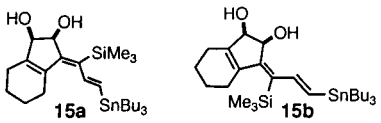
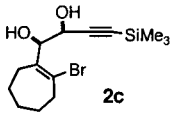
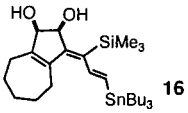
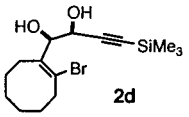
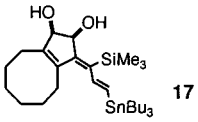
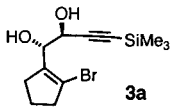
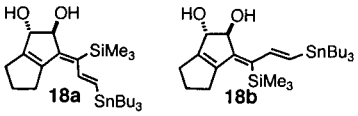
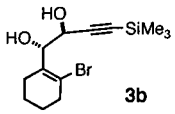
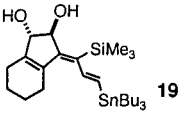
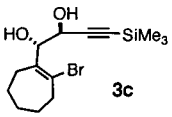
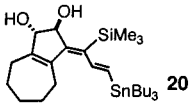
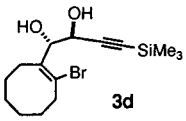
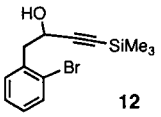
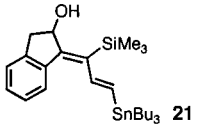
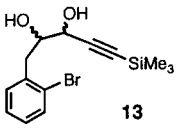
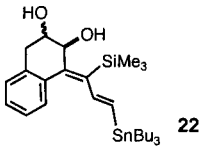
To extend the scope of the reaction and to study the role of the two hydroxy groups we investigated the cyclocarbopalladation of the anti and syn diols, protected as a dioxolane. These compounds were easily prepared by mixing the free diols with an excess of dimethoxypropane in the presence of a catalytic amount of *p*-TsOH in acetone at room tem-

(6) Bruckner, S.; Abraham, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2002**, *4*, 3391.

(7) Unambiguously assigned by NOESY experiments on the *cis*-dioxolane derivative of **2b**.

(8) Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221.

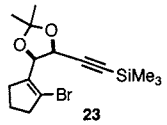
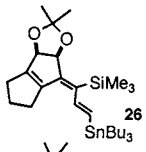
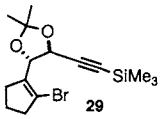
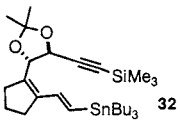
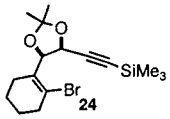
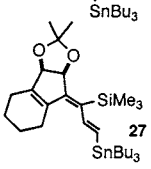
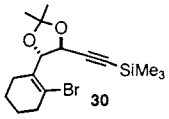
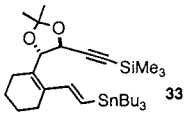
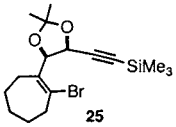
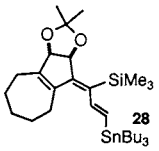
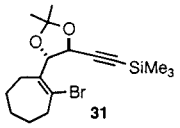
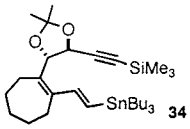
Table 1. Cyclocarbopalladation of Anti and Syn Propargylic Diols and Aromatic Propargylic Alcohols

entry	starting diol	product	time (h)	yield	ratio
1	 **2a**	 **14a** **14b**	14	75 %	78/22
2	 **2b**	 **15a** **15b**	27	71%	66/34
3	 **2c**	 **16**	16	45%	–
4	 **2d**	 **17**	23	27%	–
5	 **3a**	 **18a** **18b**	14	54 %	70/30
6	 **3b**	 **19**	25	52 %	–
7	 **3c**	 **20**	16	31 %	–
8	 **3d**	decomp.	22	–	–
9	 **12**	 **21**	16	61 %	–
10	 **13**	 **22**	16	30 %	–

perature. As expected, when dioxolanes **23**−**25** were submitted to identical reaction conditions, the tricycles **26**−**28** (Table 2, entries **1**−**3**) were obtained in acceptable yields when compared with those obtained with the unprotected diols. No isomerization of the exocyclic tetrasubstituted double bond was observed in these cases. The protected trans dioxolane **29**−**31** gave exclusively the direct Stille cross-coupling diene (entries **4**−**6**). As such as in **8**, the cyclocarbopalladation was not feasible due to the highly strained tricyclic derivatives that should be obtained in theory. As mentioned above, all the stannylated dienes are sensitive toward silica gel and give an easy protodestannation during chromatography. This problem can be avoided by treating the silica gel with a 5% solution of Et_3N in diethyl ether.

The transformation of these polycyclic compounds to many useful new structures could be envisaged considering the very different reactive groups contained in these molecules (hydroxyl, diene, tin, and trimethylsilyl).

Table 2. Cyclocarbopalladation of Trans and Cis Propargylic Dioxolanes

entry	starting diol	product	time (h)	yield	entry	starting diol	product	time (h)	yield
1	 23	 26	17	54 %	4	 29	 32	17	38 %
2	 24	 27	18	64%	5	 30	 33	20	56 %
3	 25	 28	14	48%	6	 31	 34	17	52 %

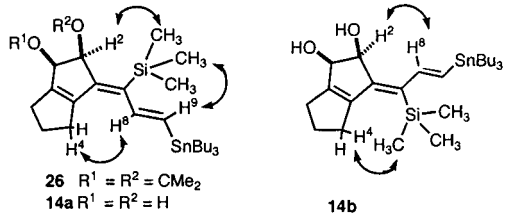


Figure 2. NOESY studies.

In conclusion, we have described an efficient way to prepare highly substituted bicyclic compounds that could be valuable intermediates in the syntheses of sophisticated biologically active natural or unnatural products. The presence of the diol function and the trimethylsilyl group on the triple bond seems to be crucial for the reaction to proceed in acceptable yields. The scope and limitations of this method are currently being investigated and the results obtained will be reported soon.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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