ORGANIC LETTERS

2003
Vol. 5, No. 6
845−848

Cyclocarbopalladation: Formation of Bicyclic 1,2-Cyclobutanediols through a Rare 4-exo-dig Cyclization

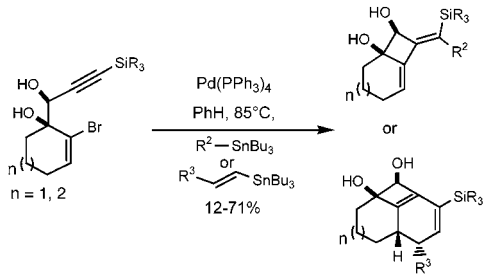
Bahaâ Salem, Philippe Klotz, and Jean Suffert*

Université Louis Pasteur de Strasbourg (UMR 7081 CNRS/ULP), Faculté de Pharmacie, 74, route du Rhin, 67401 Illkirch-Cedex, France

jeansu@aspirine.u-strasbg.fr

Received December 19, 2002

ABSTRACT



Several bicyclic compounds bearing a strained 1,2-cyclobutanediol have been prepared from a γ-bromopropargylic diol under palladium(0) catalysis. The reaction proceeds through a rare unfavored 4-exo-dig cyclocarbopalladation. In some cases, the first reaction is followed by a 6π-electrocyclization leading to unusual strained tricyclic systems.

In the past decade, a huge number of new methods using transition metals[1] for the efficient formation of carbon−carbon bonds have appeared in the scientific literature. Palladium catalysts, in particular, have been widely used and have found many applications for the formation of complex polycyclic compounds.[2] Several very elegant reactions are now available in this context.[3] In 1988, Grigg,[4] shortly followed by Negishi,[5] described a new cyclocarbopalladation process that afforded stereodefined exocyclic alkenes. The cyclizations gave acceptable yields when the substrate bearing the triple bond is an aromatic. The corresponding reaction has not been extensively investigated when acyclic[6] or cycloalkyl[7] substrates were used. The reaction generally involves an initial 5-exo-dig, 6-exo-dig, or 7-exo-dig cyclocarbopalladation followed by a terminating cross-coupling reaction with CO or various organometallic reagents. To the best of our knowledge, there is no report on the preparation of related cyclobutane derivatives through a palladium-catalyzed 4-exo-dig process using a vinyl- or alkynylstannane as the terminating trapping species. The 4-exo-dig cyclizations are unfavored according to Baldwin's rules, and only a few examples of them are known.[8,9] In a recent paper, we have disclosed a new cascade cyclization as a route to complex polycycles.[10] During the mechanistic studies of this reaction,

(1) (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (c) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596 (d) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.

(2) (a) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Wiley: New York, 1992. (b) de Meijere, A. *Chem. Rev.* **2000**, *100*, 2741−3282. (c) Tietze L.; Beifuss, U. *Angew. Chem.* **1993**, *32*, 131. (d) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

(3) For representative examples, see: (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525. (c) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem. Eur. J.* **2001**, *7*, 4035. (d) Tietze, L.; Kahle, K.; Raschke, T. *Chem. Eur. J.* **2002**, *8*, 401.

(4) (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.

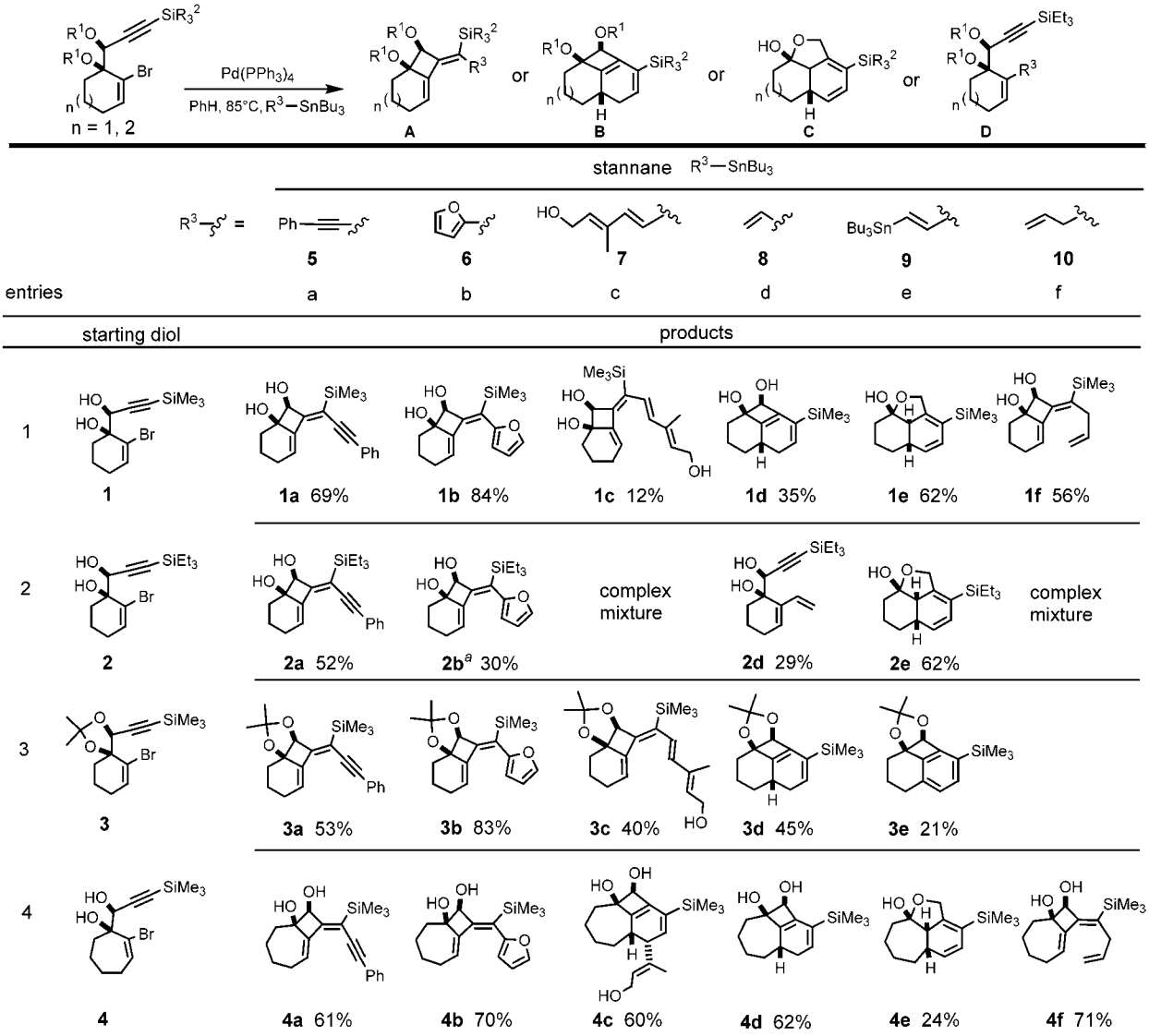
(5) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

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

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

10.1021/ol0274965 CCC: $25.00
Published on Web 02/21/2003

Table 1. Cyclocarbopalladation of Propargylic *anti* Diols

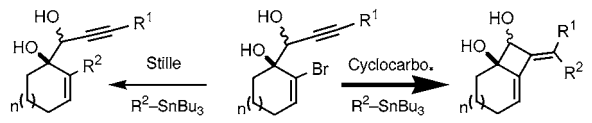


[a] 15% of the direct Stille cross-coupling compound **2b′** is also isolated (see Supporting Information).

we noticed that the final products were obtained through the rearrangement of an unusual bicyclic intermediate.

We have now developed a new access to bicyclic compounds containing a 1,2-cyclobutanediol by a rare 4-exo-dig cyclocarbopalladation of *anti*- and *syn*-propargylic 1,2-diols through Pd(0) catalysis. In the majority of the cases, the only product isolated results from the cyclocarbopalladation coupling and not from a direct Stille cross-coupling reaction (Scheme 1).

Scheme 1. Cyclocarbopalladation versus Stille Cross-Coupling Reaction



In several examples, depending on the stannylated reagents used (Table 1, when R^3 = vinyl or substituted alkenes), the original reaction is followed by a 6π-electrocyclization process (Scheme 2) to give tricyclic structures bearing a strained cyclobutene ring fused to the two other rings. These compounds are stable to chromatography on silica gel, and their structures have been assigned unambiguously by X-ray crystallographic analysis.[10]

Scheme 2. Electrocyclization

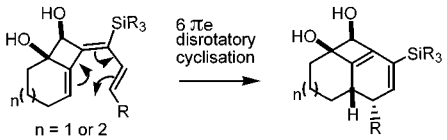
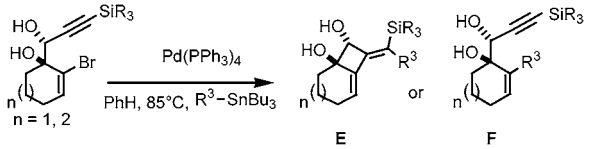


Table 2. Cyclocarbopalladation of Propargylic *syn* Diols



	stannane R^3—$SnBu_3$	
	5	**6**
entries	a	b
starting diol	products	
1	**17a** + **17a'** **17a/17a'** 52/48 49%	**17b** + **17b'** **17b/17b'** 34/66 60%
2	**18a** + **18a'** **18a/18a'** 89/11 81%	**18b** 40% –

A wide variety of reaction conditions were examined in order to optimize the yield of the bicyclic product. Ultimately, we found that with $Pd(PPh_3)_4$ (0.1 equiv) in benzene or toluene at 85 °C the reaction proceeds in acceptable yields to afford the cyclocarbopalladation products. All other catalyst systems mainly gave the Stille cross-coupling derivative with no cyclization or only decomposition of the reaction mixture. To study the scope and limitation of the reaction, a variety of propargylic bromides were tested under these reaction conditions.[11] The results of these studies are summarized in Tables 1 and 2. We first submitted propargylic diols **1**, **2**, and **4** and dioxolane **3** in racemic form possessing the *anti* relative configuration. The starting materials required for this study were prepared in a straightforward fashion and on a large scale by addition of a properly protected metalated propargylic alcohol[12] to the corresponding cyclobromoalkenones, followed by deprotection and chromatographic separation of the *anti* and *syn* diastereomers. The *anti* relative stereochemistry of the diols was established by ^1H NOESY experiments on a derivative of **1**.[13]

When diols **1**−**4** (0.3 mmol) were treated according to the conditions described above in the presence of tributylstannyl-phenylacetylene (Table 1, entries **1a**−**4a**), 2-tributylstannyl-furan (Table 1, entries **1b**−**4b**), and allylstannane (Table 1, entries **1f** and **4f**), in each case the only isolated product resulted from a 4-exo-dig addition on the bond. In most cases, no trace of the Stille cross-coupling products was observed. The bicyclic cyclobutanediols were obtained in moderate to good yields (56−84%). They are stable and can be purified by chromatography on silica gel without any precaution. Isopropylidene protection of the diol **1** to give **3** does not change the efficiency of the cyclization in two cases (entries a and b).

On the other hand, the seven-membered ring diol **4** gives **4a** and **4b** in good yields, 61% and 70%, respectively. The cyclocarbopalladation can be readily scaled up by increasing the reaction by 10-fold. For example when **1** (3 mmol, 1 g) was reacted with **6**, compound **1b** was isolated in 79% yield (0.76 g).

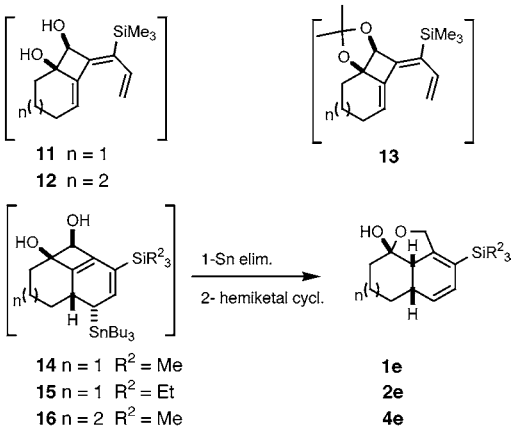
We next turned our attention to the use of vinylstannnes or dienestannanes of type **7**−**9** as terminating reagents. As expected but with a low yield (12%), **1c** was obtained starting from **1**. We observed that the sensitive diol **1c** slowly decomposes during the reaction. Replacing the trimethylsilyl group in **1** with a triethylsilyl group generates compound **2**, which gives a lower yield of **2a** (52%) and a 2/1 (30%/15%) mixture of **2b** and the corresponding Stille cross-coupling product when coupled with stannanes **5** and **6**. In addition, when diol **2** is reacted with the vinyltributylstannane **8**, compared to its homologue **1**, only a small amount of the Stille cross-coupling product **2d** (29%) is isolated, with some recovered starting material and again the absence of any cyclocarbopalladation derivatives. The use of the protected diol **3** increases the yield to 40% compared to 12% for **1c** and 45% for **3d** compared to 35% for **1d**. In contrast to the first stannylated reagents **5**, **6** and **10** that are not able to react further in a rearrangement process, stannanes **7**−**9** give unusual strained tricyclic systems with somewhat surprisingly high yields (Table 1, compounds **4c**, **3d**, **4d**, **1e**, and **2e**). They are the result of a subsequent 6π-electrocyclization of the initialy formed cyclobutanediols **11**, **12**, and **13**, (Scheme 3), which are not isolated after completion.

The reaction is stereoselective. In the case of the use of the bis-stannane **9** with the unprotected diols **1**, **2**, and **4**, the strained tricyclic compounds **14**, **15**, and **16** underwent subsequent elimination of the tin followed by an opening of the 1,2-cyclobutenediol. A final attack of the allylic oxygen on the ketone eventually afforded the hemiketals **1e**, **2e**, and **4e** in 62%, 62%, and 24% yields, respectively.[10]

These two final reactions are not possible with compound **3**, because of the protection of the two diols as a dioxolane. Thus, after the first electrocyclization, a dehydrostannation event provides the unusual aromatic tricyclic dioxolane **3e**.

To extend the scope of the reaction, experiments were investigated using the *syn* propargylic diols **17** and **18**. Applying the same reaction conditions as those used for the

Scheme 3. Postulated Intermediates



anti propargylic diol, the *syn* diols appear to possess a more versatile reactivity. In a first set of experiments only stannanes **5** and **6** were used as coupling partners. The results are summarized in Table 2. In general, lower yields of the desired cyclobutanediols were obtained with the presence of different byproducts. Diol **17** reacts with stannane **5** to give a mixture of the cyclocarbopalladation product **17a** and the Stille cross-coupling product **17a′** in a ratio of 52/48 and 49% overall yield. In a same manner, **6** gives a mixture of **17b** and **17b′** in a 34/66 ratio and 60% overall yield. The diol **18** gives a mixture of **18a**/**18a′** in a ratio of 89/11 and 81% yield and **18b** (40%) when submitted to the stannane **6**. These results indicate an important effect of the relative stereochemistry of the diol moiety, which in the *anti* diol favors the cyclocarbopalladation process, whereas the *syn* diol gives a mixture of both products. The possibility of hydrogen bonding is envisioned to explain the difference of reactivity between the two diastereomers.

In conclusion, we have shown that sequential 4-exo-dig cyclization/electrocyclization of several γ-bromopropargylic diols provides an efficient route to cyclobutanediols as well as several complex unique polycycles. The reaction proceeds in only two steps from cyclobromoalkynones.[10] Further investigations have to be performed to understand this behavior. The study of the mechanism of these reactions is underway and will be disclosed in the future.

Acknowledgment. We thank Prof. M. Harmata for stimulating discussions, the CNRS for financial support, and the MNERT (B.S.) for fellowship.

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.

OL0274965

(8) For radical 4-exo-dig cyclization, see: Bogen, S.; Fernsterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037.

(9) For an acetylenic alkyllithium 4-exo-dig cyclization, see: Bailey, W. H.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080.

(10) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107.

(11) **Typical Procedure. Cyclocarbopalladation of γ-Bromopropargylic Diol.** The reaction is carried out in an oven-dried 25-mL bicol, equipped with a reflux condenser, under argon atmosphere. To a solution of the substrate (**1**, **2**, **3**, **4**, **17**, or **18**; 0.3 mmol, ≈100 mg, 1 equiv) in 10 mL of dried benzene was added $Pd(PPh_3)_4$ (0.1 equiv, 10 mol %), followed by the stannylated reagent (1.3 equiv). The reaction mixture was stirred for 1−17 h in a preheated 90 °C oil bath. The reaction was followed by TLC. Then, the reaction mixture was concentrated in vacuo and immediately purified by flash chromatography, leading to the different bicyclic cyclobutan-1,2-diols.

(12) (a) Ushida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *32*, 2941−2942. (b) Suffert, J.; Toussaint, D. *Tetrahedron Lett.* **1997**, *38*, 5507−5510.

(13) See supporting Information of ref 10.