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Cyclocarbopalladation: Sequential Cyclization and C–H Activation/Stille Cross-Coupling in the Pd-5-*Exo*-*Dig* Reaction

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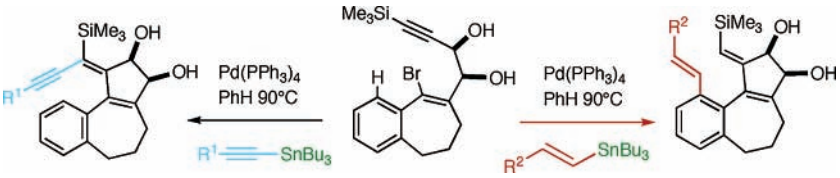
ABSTRACT

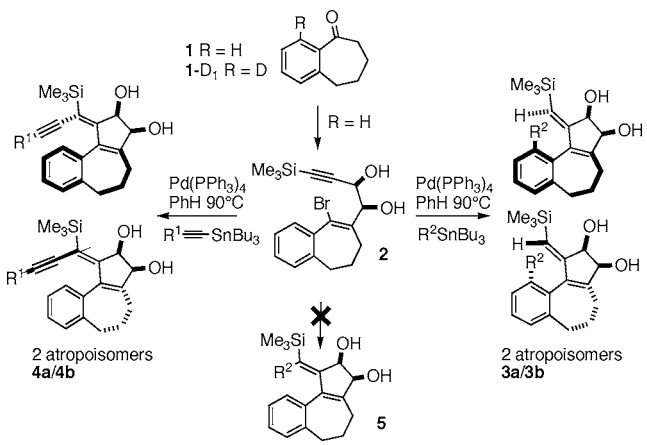


A new cyclization and C–H activation/Stille cross-coupling reaction on a nonactivated aromatic has been discovered. The reaction is regioselective and controlled by the stannylated reagent. Labeling experiments have been performed that provide evidence for a complete transfer of the deuterium through the coordination sphere of palladium.

The discovery of new C−H activation processes, especially for the functionalization of nonactivated aromatic derivatives, constitutes an extremely important direction in metal-catalyzed organic chemistry. Significant results have been obtained for the activation of aromatic C−H bonds with palladium.[1] Larock[2] recently demonstrated the potential of this reaction in the preparation of fused polycycles via multiple C−H activation. We have previously reported that 4- and 5-*exo*-*dig* cyclocarbopalladation can be used for the elaboration of highly functionnalized bicyclic systems.[3] This multistep reaction terminates with a Stille cross-coupling and proceeds overall with acceptable to good yields. The 5-*exo*-*dig* cyclization has not been investigated with cycloalkyl substrates bearing an aromatic moiety.

In pursuit of previous investigations in this field, we envisaged that the *anti*-propargylic-1,2-diols **2** derived from benzosuberone **1** would undergo an efficient 5-*exo*-*dig* carbocyclopalladation producing the basic 5−7−6 core

Scheme 1



(1) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533. (c) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(2) (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (c) Larock, R. C.; Tian, Q. *Org. Lett.* **2000**, *2*, 3329. (d) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372.

(3) (a) Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826. (b) Salem, B.; Klotz, P.; Suffert, J. *Synthesis* **2004**, *2*, 298. (c) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845. (d) Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 2307. (e) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107.

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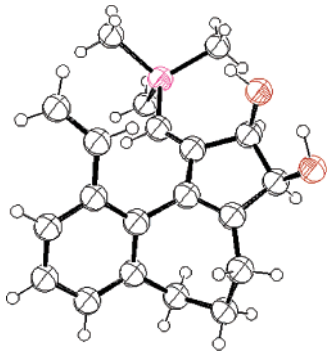
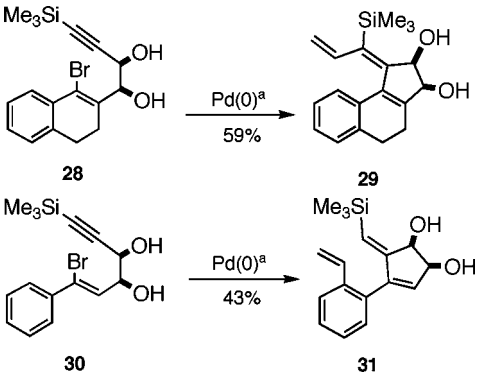


Figure 1. ORTEP of compound **17**.

structures of several natural products including phorbol[4] and tintinnadiol[5] as well as synthetic derivatives that possess biological activities for the treatment of osteoporosis and arteriosclerosis.[6]

We initially focused on the use of vinyl, allyl, or heteroaromatic tributylstannanes as final coupling partners. Surprisingly, when compound **2** was treated with vinyltributylstannane at 90 °C in benzene in the presence of $Pd(PPh_3)_4$ (10% mol), none of the expected product **5** was obtained (Scheme 1). After extensive NMR experiments and X-ray structure analysis[7] (Figure 1), the final structure of the product was determined to be the styrene derivative **17** (Table 1). The CH activation reaction is mainly limited to the use of benzosuberone derivatives. Similar treatment of the diol **28** prepared from tetralone gave only the direct Stille cross-coupling derivative **29** in 59% yield (Scheme 2). When these conditions are applied on the acyclic diol **30**, the CH activation still proceeds and the product **31** is isolated in 43% yield, opening the scope of the reaction (Scheme 2).

Scheme 2

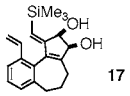
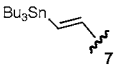
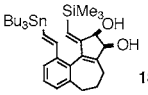
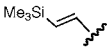
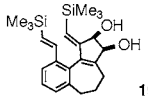
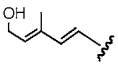
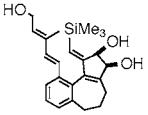
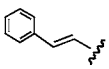
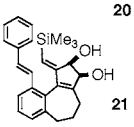
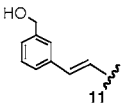
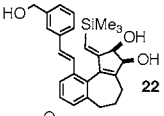
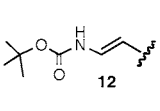
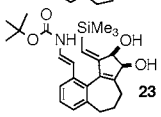
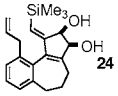
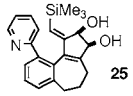
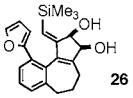
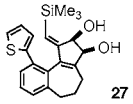


[a] The reaction was performed under microwave irradiation.

The C−H/Stille cross-coupling termination is general with a variety of stannylated derivatives **6**−**16** affording products

(4) Pettersen, R. C.; Ferguson, G. *Chem. Commun.* **1967**, 716.
(5) Engler, M.; Anket, T.; Stener, O. *Phytochemistry* **1998**, *49*, 2591.
(6) Carniato, D.; Gadeck, T.; Gourvest, J.-F.; Knolle, J.; McDowell, R.; Peyman, A. WO Patent 99/15506, 1999.

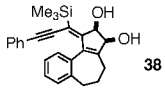
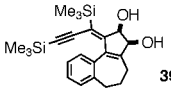
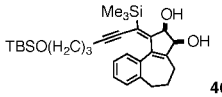
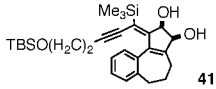
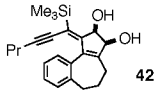
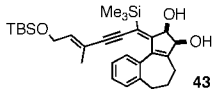
Table 1. Synthesis of Polycycles via Palladium CH Activation/ Stille Cross-Coupling Termination with Vinyl, Hetoraromatic, or Allylstannanes

entry	R^2-SnBu$_3$	product	time (h or min)	% yield
1	 **6**	 **17**	8 h	70
2	 **7**	 **18**	5 h	58
3	 **8**	 **19**	18 h 18 min	30 70[a]
4	 **9**	 **20**	30 min	45
5	 **10**	 **21**	18 h 10 min	21 45[a]
6	 **11**	 **22**	18 h	61
7	 **12**	 **23**	18 h	65
8	 **13**	 **24**	20 h	52
9	 **14**	 **25**	20 h	0 53[b]
10	 **15**	 **26**	54 h	48
11	 **16**	 **27**	24 h 30 min	13 53[a]

17−**27** in yields ranging up to 70% (Table 1). In some cases the use of microwave irradiation greatly increased the yields and shortened the reaction time. For example, when **2** was treated with stannane **8**, compound **19** was obtained in 70% yield under microwave irradiation in 18 min but only in 30% yield after 18 h under conventional conditions. Heteroaromatic derivatives **25**−**27** are also accessible using this method.

It is noteworthy that products **17**−**27** are all obtained as a mixture of atropoisomers **3a**/**3b** as clearly suggested by the ^{1}H and ^{13}C NMR spectrum. All attempts to separate both isomers by chromatography were thwarted by the rapid

Table 2. Synthesis of Polycycles via Cyclocarbopalladation/Stille Cross-Coupling with Alkynylstannanes at the Terminal Vinylic Position

entry	R^1—≡—$SnBu_3$	product	time (h)	% yield
1	Ph— **32**	 **38**	12	58
2	Me_3Si— **33**	 **39**	5	45
3	$TBSO(H_2C)_3$— **34**	 **40**	8	54
4	$TBSO(H_2C)_2$— **35**	 **41**	8	48
5	Pr— **36**	 **42**	18	75
6	TBSO— **37**	 **43**	0.5	23

equilibration of the isomers at room temperature. Moreover, when diol **2** was submitted to the same reaction conditions, but in the presence of the alkynylstannanes **32**−**37**, the only products isolated (**38**−**43**) came from the final Stille cross-coupling on the silylated exocyclic double bond (Table 2).

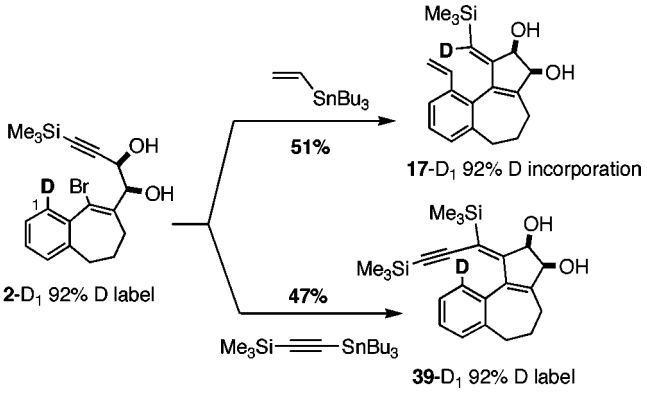
All alkynylstannanes tested gave the product regioselectively as a mixture of inseparable atropoisomers **4a**/**4b** as exemplified in Table 2. Therefore, the regioselectivity of the final coupling is totally substrate dependent.

To study the mechanism of this new C−H activation process, the labeled diol **2**-D_1 was prepared from benzosuberone **1**-D_1 using a modified labeling procedure described by Herbert.[8] Deuterium incorporation (92%) was determined

(7) Crystal data for **17**: $C_{20}H_{26}O_2Si$, M_r = 326.52, monoclinic, space group *C*1/*c*1, a = 18.3268(6) Å, b = 10.5670(3) Å, c = 9.6519(4) Å, β 95.627(5)°, V = 1860.2(1) Å^3, Z = 4, ρ_{calcd} = 0.17 g·cm^{-3}, μ = 0.134 mm^{-1}, 7220 data (2491 reflections with $I > 3\sigma(I)$), R = 0.045, wR = 0.054, residual electron density extrema ±0.234 e Å^{-3}. Measurements were collected on a Kappa CCD diffractometer (Mo Kα, graphite monochromated, λ = 0.71073 Å). These structures were solved using direct methods. After refinement of the non-hydrogen atoms, difference Fourier maps revealed maxima of residual electron density close to positions expected for hydrogen atoms. Hydrogen atoms were introduced as fixed contributors at calculated positions (C−H = 0.95 A, B(H) = 1.3 Bequiv). Final difference maps revealed no significant maxima. All calculations were done using the Nonius OpenMoleN package. Neutral atom scattering factor coefficients and anomalous dispersion coefficients were taken from a standard source. CCDC 240661 (**17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

(8) Ellames, G. J.; Gibson, J. S.; Herbert, J. M.; McNeill, A. H. *Tetrahedron* **2001**, *57*, 9487.

Scheme 3

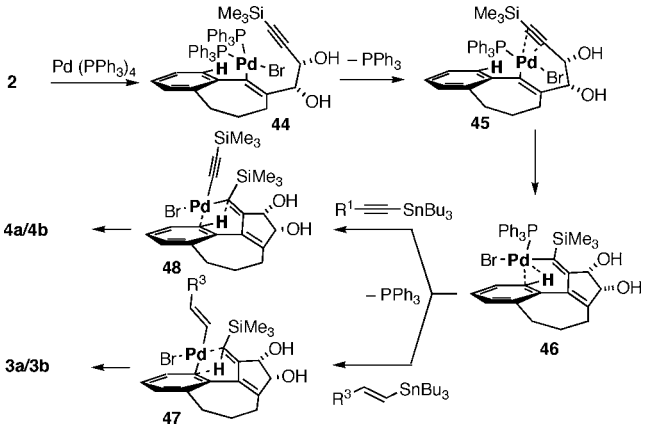


by integration of the H-4 aromatic proton signal of the labeled **1**-D_1/nonlabeled **1** (Scheme 3).

When compound **2**-D_1 was treated under the conditions used above with vinylstannane **6**, **17**-D_1 was isolated as the sole product in 51% yield with 92% deuterium incorporation. Similarly **2**-D_1 gave **39**-D_1 in 47% yield as the sole product with no D transfer. This fact strongly suggests that the D atom is transferred to the terminal vinyl silane through the coordination sphere of palladium.

The reaction sumerized in Table 1 can be interpreted according to Scheme 4. The sequence is initiated by the

Scheme 4



insertion of palladium(0) into the vinylic C−Br bond giving **44** that, after elimination of the first PPh_3 affording **45** followed by cyclocarbopalladation of the triple bond, leads to the intermediate **46**. At this stage, the palladium must strongly interact with the aromatic C−H bond through an agostic interaction. Probably due to stereoelectronic factors, **46** reacts directly with the stannylated alkyne derivatives with the loss of a second PPh_3 giving **48** and ending in final insertion of the triple bond on the vinylic position to give products **4a**/**4b**.

When a vinylic, heteroaromatic or allylic stannylated reagent is used instead, the palladacycle in **47** reacts

preferentially on the aromatic position with a clean and total transfer of the H-1 hydrogen on the vinylic position. This unexpected behavior is under investigation.

In conclusion, a new C−H activation of nonactivated aromatics has been discovered. The reaction is regioselective and controlled by the stannylated reagent. DFT calculations and other experiments are in progress to understand this reaction and to study its scope and limitations.

Acknowledgment. We thank the CNRS for financial support and the MNERT (C.B.) for a fellowship.

Note Added after ASAP Publication. Parts c and d of ref 2 were not included in the version published ASAP January 22, 2005. The corrected version was published ASAP January 27, 2005.

Supporting Information Available: Experimental procedures, physical data, and NMR spectra for **1**D_1-**43** and synthetic intermediates and X-ray data for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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