ORGANIC LETTERS

2013
Vol. 15, No. 3
582–585

Increasing the Efficiency of the Transannular Diels–Alder Strategy via Palladium(II)-Catalyzed Macrocyclizations

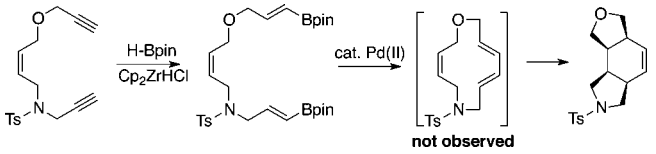
Robert G. Iafe, Jonathan L. Kuo, Dustin G. Hochstatter, Tomomi Saga, Jonathan W. Turner, and Craig A. Merlic*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

merlic@chem.ucla.edu

Received December 12, 2012

ABSTRACT



Palladium(II)-catalyzed macrocyclizations of bis(vinylboronate ester) compounds are demonstrated to provide a strategically efficient approach to transannular Diels–Alder reaction substrates. In several systems reported, the macrocycle is preorganized such that cycloaddition at room temperature occurs concomitantly with cyclization. Numerous advantages over palladium(0)-catalyzed cross-coupling approaches are demonstrated.

Transannular Diels–Alder (TADA) reactions are a topologically powerful synthetic strategy for the construction of polycyclic ring frameworks[1] and have been utilized in the synthesis of complex targets.[2] They can exhibit stereoselectivity not attainable in inter- or intramolecular Diels–Alder reactions as elegantly demonstrated by Roush and co-workers.[3] Remarkably, the first characterized Diels–Alderase enzyme catalyzes a TADA reaction.[4] The challenge for chemists, though, is synthesis of the requisite macrocyclic TADA substrate. Macrocyclization is the crucial issue, and geometric constraints often preclude S_N2 type substitutions as the key bond-forming step. Palladium(0)-catalyzed cross-couplings are widely used for macrocyclizations and also for formation of strained rings[5] and, thus, can be applied toward the synthesis of TADA substrates. Indeed, Deslongchamps demonstrated the utility of Stille macrocyclizations as the key synthetic strategy for the preparation of macrocyclic trienes.[6] That approach was developed to solve the key problem of "The bottleneck of the TADA strategy resides in the macrocyclization step."[6]

Unfortunately, Pd(0)-catalyzed cyclization strategies are not without limitations. Vinyl halide intermediates can be toxic or carcinogenic, Pd(0) reactions require an inert atmosphere, complex ligands can be necessary to promote oxidative addition, and heating is often required which can preclude isolating strained structures. Most importantly, macrocyclization substrates must have the end groups differentiated into electrophilic (i.e., vinyl halide) and nucleophilic (i.e., vinyl metal) components. Inevitably that requirement translates into lengthy synthetic pathways.

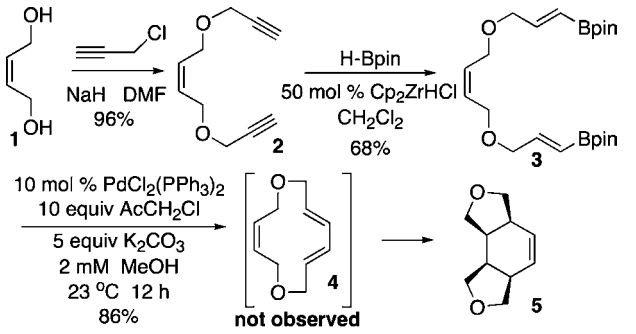
We developed Pd(II)-catalyzed cross-coupling reactions of vinylboronate esters as a solution to the problems inherent in Pd(0)-catalyzed cross-couplings.[7] Our approach efficiently prepares cyclic targets in just two steps from α,ω-diynes. We report herein on the development and application of Pd(II)-catalyzed macrocyclizations as a strategically efficient approach to prepare TADA substrates.

(1) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831.
(2) For reviews, see: (a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (b) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243. See also: (a) Li, Y.; Pattenden, G. *Tetrahedron Lett.* **2011**, *52*, 2088. (b) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722.
(3) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818.
(4) Kim, H. J.; Ruszczycky, M. W.; Choi, S.-H.; Liu, Y.-N.; Liu, H.-W. *Nature* **2011**, *473*, 109.
(5) (a) Shimamura, H.; Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776. (b) Qian, H.; Yue, W.; Zhen, Y.; Di Motta, S.; Di Donato, E.; Negri, F.; Qu, J.; Xu, W.; Zhu, D.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 6275. (c) Palmer, W. S.; Woerpel, K. A. *Organometallics* **1997**, *16*, 4824.
(6) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317.
(7) Iafe, R. G.; Chan, D. G.; Kuo, J. L.; Boon, B. A.; Faizi, D. J.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2012**, *14*, 4282.

10.1021/ol303394t
Published on Web 01/23/2013

Dialkylation of *cis*-2-butene-1,4-diol provided ene-diyne **2**, and hydroboration with pinacolborane catalyzed by Schwartz's catalyst using the Srebnik procedure[8] gave bis-(vinylboronate ester) **3** as the macrocyclization substrate (Scheme 1). A Pd(II)-catalyzed reaction using 10 mol % palladium(bistriphenylphosphine)dichloride, an aqueous potassium carbonate activator for boron, and chloroacetone as the reoxidant in methanol solvent at room temperature for 12 h gave tricycle **5** resulting from a tandem cyclization/TADA sequence as the only observable product in 86% yield. Cyclization at 60 °C reduced the yield to 42% due to competing protodeboronation. Thus, reduced temperatures are preferred and also have strategic advantages (*vide infra*).

Scheme 1. Pd(II)-Catalysis Applied to a TADA Reaction



The stereochemistry of **5** is proposed based on density functional theory calculations at the B3LYP/6-31G* level[9] using the Gaussian 09 package,[10] which is known to be effective for explaining reaction stereoselectivities.[11] Calculations on the endo and exo Diels–Alder transition state structures of **4** identified two global stationary transition states (Figure 1). The endo transition state leading to the cis-syn-cis product is predicted to be 3.54 kcal/mol lower in energy, which corresponds to a greater than 99.7:0.3 selectivity. Indeed, no evidence of any other diastereoisomer was detected by TLC or NMR. The large difference in transition state energies can be attributed to the preference for a staggered conformation with respect to forming bonds, or torsional steering.[12]

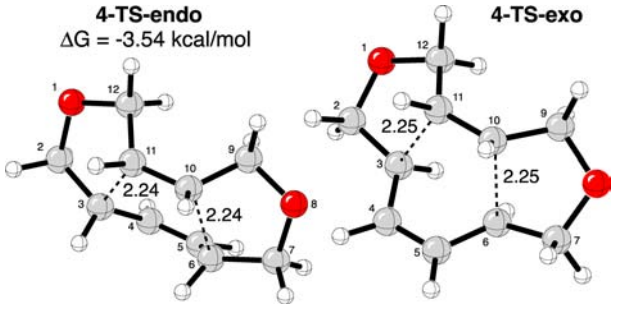
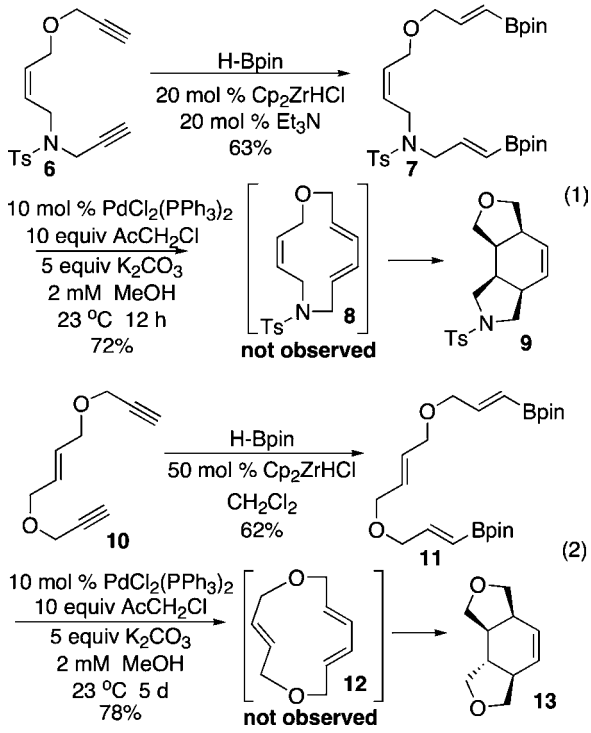


Figure 1. Calculated endo and exo transition state structures for TADA reaction of **4** to **5**.

Starting again from *cis*-2-butenediol, monoalkylation and Mitsunobu substitution readily provided diyne **6** and hydroboration gave substrate **7**.[13] Pd(II)-catalyzed macrocyclization under the standard conditions gave a single diastereomer **9** resulting again from a tandem cyclization/TADA sequence in 72% yield (eq 1). Using a similar synthetic path as that for **3**, but starting from *trans*-2-butene-1,4-diol, substrate **11** was constructed. Cyclization of **11** yielded **13** in 78% yield (eq 2). In this instance 5 days were required for the reaction to proceed to completion. Calculations on the TADA transition state for **12** found the activation energy to be 1.26 kcal/mol lower than that for **4**, so the increased reaction time was due to the palladium-catalyzed step and not the TADA step.

12-Membered trienes **4**, **8**, and **12** were not observed during the reactions likely due to conformational preorganization for the TADA reaction.[14] Notable is that the dienes and dienophiles were not activated with electron-donating or -withdrawing substituents. Such proximity-induced[14] reactivity in TADA reactions was first reported by Deslongchamps.[15]



(8) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. Some substrates used a modified protocol: Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777.

(9) B3LYP: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. 6-31G*: (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acta* **1973**, *28*, 213.

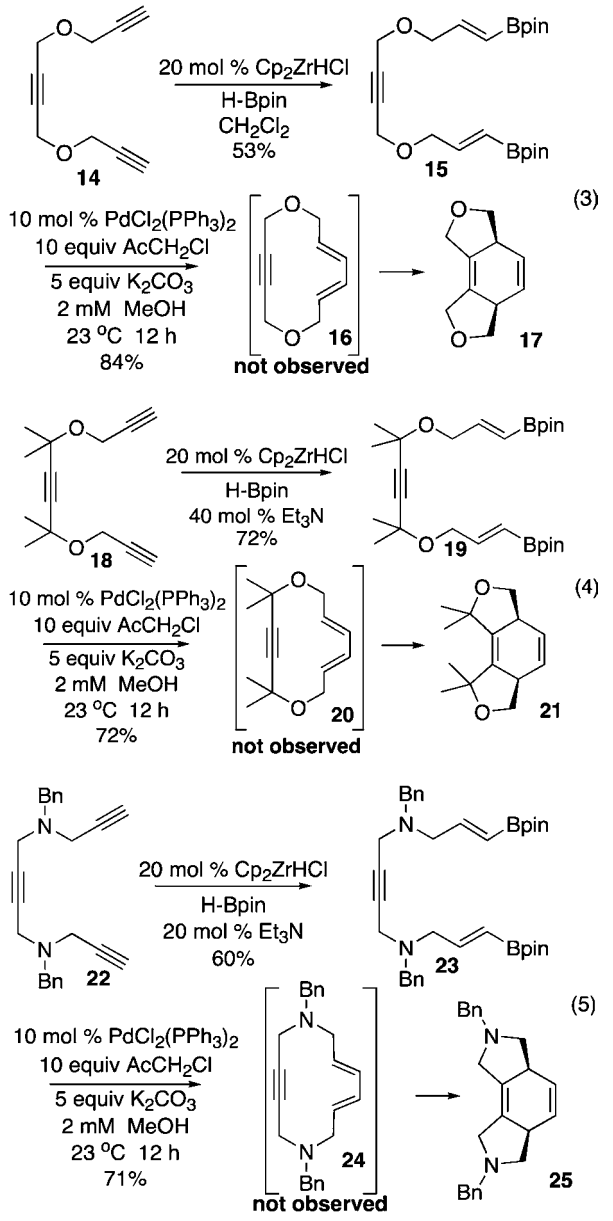
(10) Calculations were performed with Gaussian 09 (Frisch, M. J., et al.); see Supporting Information for full reference.

(11) (a) Um, J. M.; Houk, K. N.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 3769. (b) Iafe, R.; Houk, K. N. *Org. Lett.* **2006**, *8*, 3469. (c) Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Catal.* **2004**, *346*, 1175.

(12) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513. (c) Iafe, R. G.; Houk, K. N. *Org. Lett.* **2006**, *8*, 3469 and references therein.

A benefit of Pd-catalyzed cyclizations is the ability to prepare strained ring systems.[5] In such processes, the precursor to the strained target is a larger ring palladacycle. Given the larger ring size and longer Pd−C bonds, typically on the order of 2 Å for Pd−C(sp^2) bonds, the palladacycle is not as strained and so is readily formed. Subsequent reductive elimination forms the desired strained product. To further increase the ring strain of the intermediate macrocycle, we explored three 12-membered TADA substrates containing alkyne dienophiles.

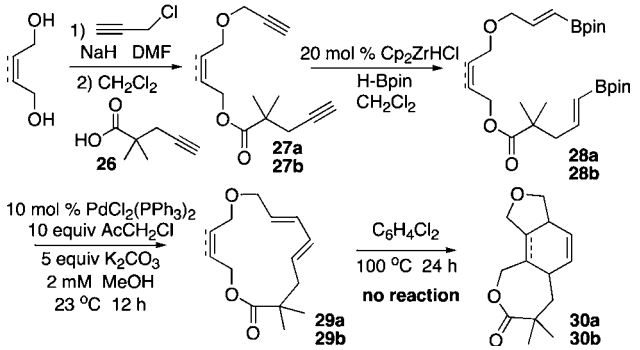
Dialkylation of 2-butyne-1,4-diol provided triyne **14** and hydroboration yielded cyclization substrate **15** (eq 3).[13] A Pd(II)-catalyzed reaction led to tricycle **17** in 84% yield as the result of a tandem cyclization/TADA process. A similar sequence starting from 2,5-dimethyl-3-hexyne-2,5-diol produced tricycle **21** (eq 4). Finally, dialkylation of 1,4-dibromo-2-butyne with benzylpropargylamine gave triyne **22** that was carried forward under the standard conditions to provide tricycle **25** in 71% yield (eq 5). As with all of the 12-membered trienes, no macrocyclic dienyne intermediates were observed.



Products **17**, **21**, and **25** contain dihydrobenzene rings, so it might be expected to be subject to aromatization via hydrogen loss under oxidizing conditions. In practice, high yields for products were obtained and aromatized products were not observed. This is an advantage of being able to perform Pd(II)-catalyzed cyclizations at room temperature in contrast to other types of cyclizations which typically require heating. In fact, heating product **17** in air at a mere 60 °C started aromatization.

Next we turned to larger ring TADA triene and dienyne targets. Monoalkylation of *cis*-2-butene-1,4-diol and DCC coupling with acid **26** provided diyne **27a** which was hydroborated to yield substrate **28a** (Scheme 2).[13] Pd(II)-catalyzed macrocyclization of **28a** afforded triene **29a**, and tricycle **30a** was not detected. In an attempt to execute the TADA reaction, **30a** was heated at 100 °C for 24 h, but no TADA product was seen. In contrast with macrocycles **4**, **8**, and **12** that were primed for TADA reaction, macrocycle **29a** may not readily attain the conformation required for cycloaddition. Such lack of reactivity has been observed in a TADA system.[16] In an exactly analogous series of transformations,[13] 2-butyne-1,4-diol was converted to macrocycle **29b**. Even with the more geometrically constrained alkyne unit in **29b**, a TADA reaction was not observed.

Scheme 2. Macrocyclic Triene **29a** and Dienyne **29b**



As a direct head-to-head comparison of the efficiency of our Pd(II)-catalyzed macrocyclization strategy versus a Pd(0)-catalyzed Stille strategy for TADA substrate synthesis, we examined a specific target prepared by Deslongchamps.[6] As a component of extensive studies on TADA reactions, Deslongchamps reported using Stille

(13) See Supporting Information.

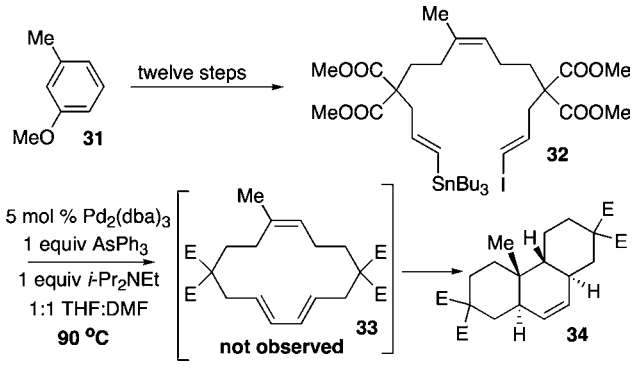
(14) Krenske, E. H.; Perry, E. W.; Jerome, S. V.; Maimone, T. J.; Baran, P. S.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3016.

(15) Berube, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255.

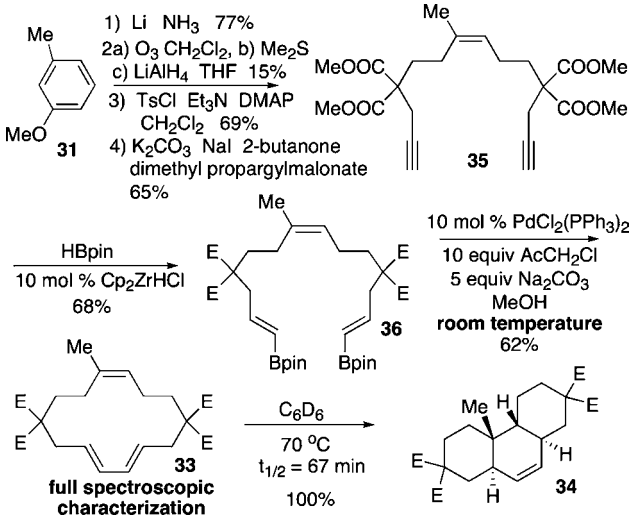
(16) Jung, M. E.; Zhang, T.-H.; Lui, R. M.; Gutierrez, O.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 6933. See also: Boeckman, R. K.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1792.

(17) An alternate synthesis of **33** via alkylation at 80 °C also yielded **34** instead. Ndibwami, A.; Lamothe, S.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 714.

Scheme 3. Deslongchamps Transannular Diels–Alder System[6]



Scheme 4. Improved Transannular Diels–Alder System Using Pd(II)-Catalysis



reactions as an effective entry to macrocyclic trienes, and one system is shown in Scheme 3. In the pivotal Pd(0)-catalyzed macrocyclization of substrate **32**, prepared in 12 steps, macrocyclic triene **33** was not observed and, instead, TADA product **34** was obtained. A potential reason macrocyclic triene **33** was not seen is that the reaction was performed at 90 °C.[17]

We applied our Pd(II)-catalyzed macrocyclization strategy to the identical target (Scheme 4). Starting also from 3-methylanisole (**31**), Birch reduction, selective reductive ozonolysis, tosylation, alkylation, and hydroboration afforded substrate **36** in just five steps. Pd(II)-catalyzed macrocyclization at rt cleanly yielded triene **33**. Triene **33** was sensitive, but unlike Deslongchamps, we were able to characterize it fully by spectroscopic means. Furthermore, we were able to observe the TADA reaction in real time and study the reaction kinetics.[18] Heating **33** at 70 °C in benzene-d_6 converted it to TADA product **34** with a half-life of only 67 min. Thus, it is apparent why Deslongchamps did not observe the macrocycle from the Pd(0)-catalyzed reaction at 90 °C.

In conclusion, we demonstrated a rapid and efficient strategy for the synthesis of transannular Diels–Alder cycloaddition macrocycles using Pd(II)-catalyzed cyclizations of bis(vinylboronate ester) substrates at rt. Nine systems were prepared, and a direct comparison example demonstrated the remarkable efficiency of this protocol. Six systems reacted by an intriguing tandem cyclization/TADA sequence due to conformational preorganization favoring proximity-induced cycloaddition that is currently under further study. The examples herein employed *E,E*-dienes, but *E,Z*- and *Z,Z*-dienes are also accessible,[7] making this a powerful strategy.

Acknowledgment. We thank the ACS Petroleum Research Fund for support of this research. J.L.K. was supported by the Amgen Scholars and Howard Hughes Undergraduate Research Fellowship programs.

Supporting Information Available. Experimental procedures, spectral data for all new compounds, and calculated geometries and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For computational studies on transition state structures and energies for TADA reactions of 14-membered trienes, see: (a) Prathyusha, V.; Ramakrishna, S.; Priyakumar, U. V. *J. Org. Chem.* **2012**, *77*, 5371. (b) Wolfe, S.; Buckley, A. V.; Weinberg, N. *Can. J. Chem.* **2001**, *79*, 1284.

The authors declare no competing financial interest.