Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8149–8152

Palladium-mediated transannular cyclizations of medium-ring olefinic enolsilanes

Andrew S. Kende,[a,*] Clara E. Mota Nelson[b] and Sébastien Fuchs[a]

[a]*Department of Chemistry, University of Rochester, PO Box 270216, Rochester, NY 14627, USA*
[b]*PPG Industries Inc., Allison Park, PA 15101, USA*

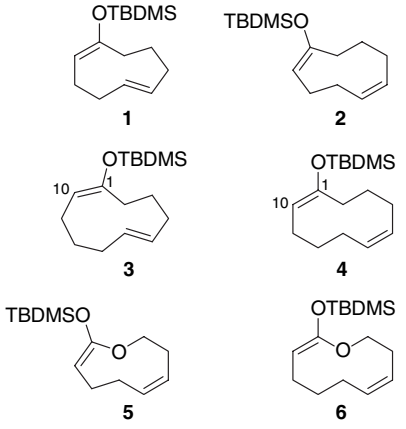
Received 14 September 2005; revised 19 September 2005; accepted 20 September 2005
Available online 7 October 2005

Abstract—Medium-ring olefinic ketone and lactone enolsilanes were subjected to palladium(II)-mediated cycloalkenylation conditions. Diverse bicyclic ring products were obtained in moderate to good yields. The effect of olefin geometry and ring size is discussed.

Palladium(II)-mediated cyclization of olefinic enol ethers is a powerful and reasonably general method for cycloalkenylation reactions in which a new carbon–carbon bond is formed from the enolic center to an alkene. First observed by Saegusa et al. in 1979,[1] this reaction was soon shown to be an efficient route to numerous bridged and spirocyclic bicycloalkenones[2] and subsequently exploited as a key step in the synthesis of several natural products.[3]

While the scope of these palladium-mediated cycloalkenylations has been the subject of several detailed surveys,[4] we are unaware of such cyclizations in which both the enolsilane and the olefin are in the same ring. We now report the course of such reactions in selected medium-ring enolsilanes represented by the cyclononadienes **1** and **2**, the cyclodecadienes **3** and **4**, and the lactone derivatives **5** and **6** (Scheme 1).

The olefinic ketone precursors to enolsilanes **1**–**4** were prepared by known procedures.[5] The olefinic lactone precursors **12** and **13** to ketene acetals **5** and **6** were obtained by macrolactonization, after semi-hydrogenation of the readily available ω-hydroxyalkynoic acids **7** and **8** (Scheme 2).[6] Each ring system required a different lactonization method to achieve sufficient yields of the very volatile lactone products.[7]



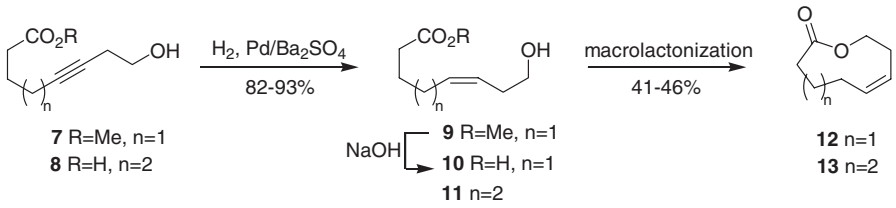
Scheme 1.

Whereas the silylations[8] of symmetrical nine-membered ketone precursors to **1** and **2** can form only one possible enolsilane regioisomer, the 10-membered ketones are known to undergo regioselective silylation in the 1,10 position.[9] The silylations of the macrolactones **12** and **13** were carried out in a slightly different manner.[10]

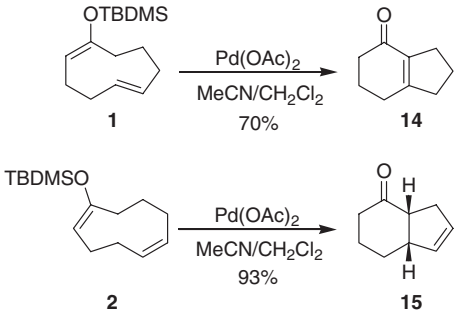
The transannular cyclizations[11] of the 2 nine-membered enolsilanes **1** and **2** using stoichiometric $Pd(OAc)_2$ led, respectively, to two different bicyclo[4.3.0]ketones in good yields (Scheme 3). (*E*)-Cycloalkene enolsilane **1** produced the α,β-unsaturated ketone **14**,[12] whereas the (*Z*)-cycloalkene enol silyl ether **2** led to the *cis*-bicycloalkenone **15**.[13]

Keywords: Palladium(II)-mediated cycloalkenylation; Cyclization; Medium-ring enolsilanes; Bicyclic ketones/lactones.
* Corresponding author. Tel.: +1 585 275 4236; fax: +1 585 276 0205; e-mail: kende@chem.rochester.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.125



Scheme 2.

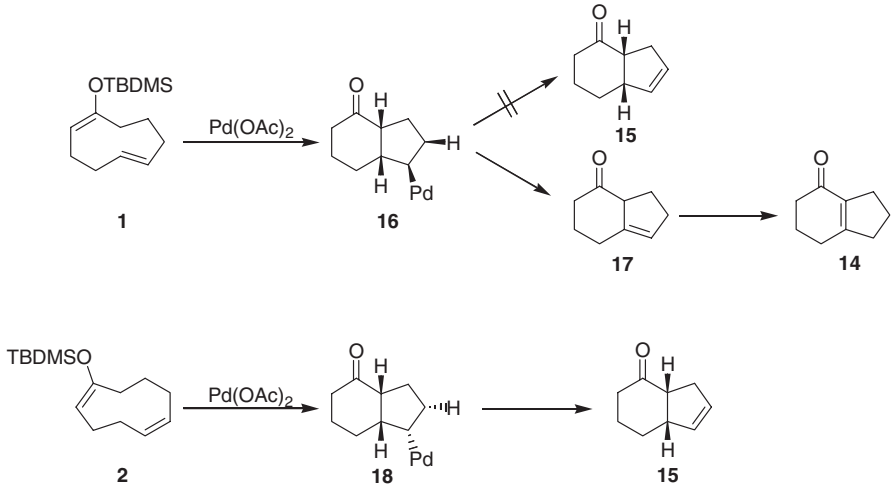


Scheme 3.

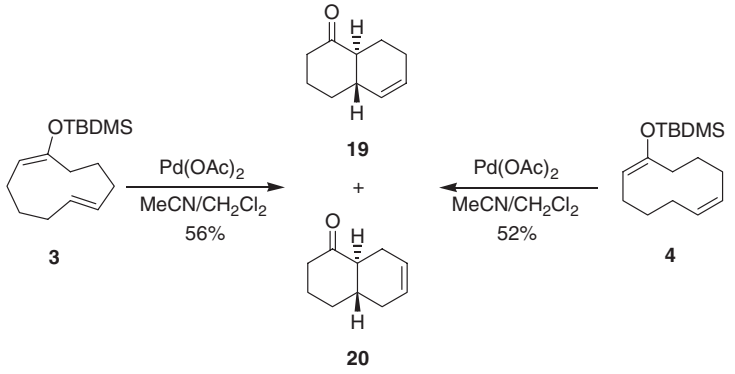
The observed regioselectivities in the above reactions are consistent with the mechanism we had previously envisioned for the palladium(II)-mediated cycloalkenylation.[3a,14] As recently reiterated by Toyota and Ihara,[4a] this mechanism comprises a backside nucleophilic attack by the double bond of the enol-TBS derivative upon the Pd-coordinated exocyclic olefin.[15] Examination of Dreiding models of the substrates **1** and **2** during cyclization predicts that they should lead, respectively, to two different sigma-bonded palladium intermediates, namely **16** and **18** (Scheme 4). In the case of the bicyclic intermediate **16**, in which two hydrogens are available for *syn* palladium β-hydride elimination,[16] the ketone **17** appears to form, which by subsequent enolization, gives the α,β-unsaturated ketone **14** as the only isolated product. On the other hand, the bicyclic intermediate **18**, with the palladium *anti* to the hydrogen of the ring junction, leads upon *syn* palladium β-hydride elimination to the bicycloalkenone **15**.

For the 10-membered ring substrates **3** and **4**, both (*E*)- and (*Z*)-cycloalkenes produced the *trans*-bicyclo-[4.4.0]ketones **19**[17] and **20**[18] in moderate yields (Scheme 5). These regioisomeric products were obtained in different ratios depending on the olefin geometry of the substrates. Thus, the cyclization of the (*E*)-cycloalkene enolsilane **3** gave compounds **19** and **20** in a ratio of 1:1.3, whereas the (*Z*)-cycloalkene enolsilane **4** produced these compounds in a 7.5:1 ratio.

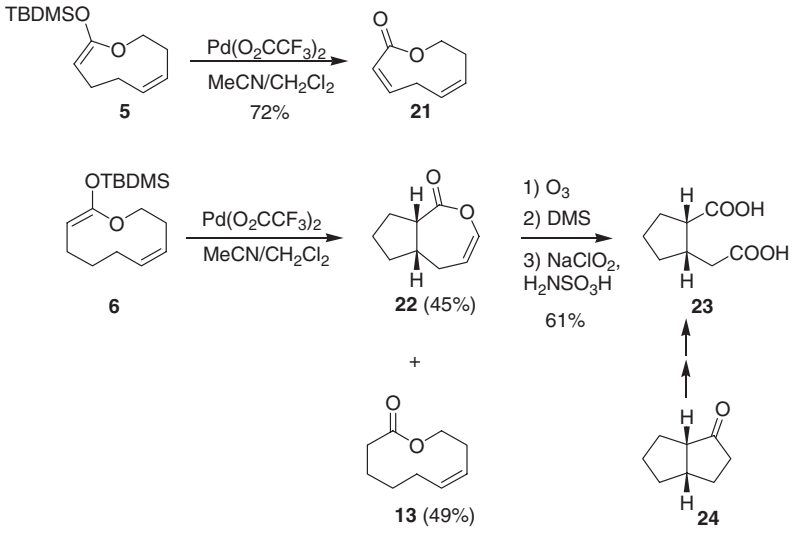
Palladium(II)-mediated cyclization was unsuccessful when ketene acetals **5** and **6** were treated with $Pd(OAc)_2$. Only starting ketene-acetal was recovered after 16 h. The reaction was then carried out with the more electrophilic palladium trifluoroacetate instead of palladium acetate. Under these conditions, the reaction product depended dramatically on ring size (Scheme 6). For the nine-membered reactant **5**, the sole product was the α,β-unsaturated lactone **21**.[19] Such dehydrogenation is a well established side reaction of certain enolsilanes under $Pd(OAc)_2$ treatment.[1] In the case of the 10-membered ketene acetal **6**, $Pd(O_2CCF_3)_2$ treatment led to the bicyclic enol lactone **22**[20,21] and recovered lactone **13**. The structure of **22** was established by 500 MHz ^1H NMR through extensive decoupling of each ring proton and by oxidative degradation to the known *cis* cyclopentane diacid **23**.[22] This diacid had identical melting point, IR, ^1H, and ^{13}C NMR spectra with an authentic sample



Scheme 4.



Scheme 5.



Scheme 6.

of **23** independently prepared from the readily available ketone **24**.[23,24]

Our results suggest that such transannular cycloalkenylations in certain medium rings are reasonably efficient and offer potential as a strategic element in the synthesis of polycyclic natural products.

References and notes

1. Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494–496.
2. Kende, A. S.; Roth, B.; Sanfilipo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784–1785; Kende, A. S.; Battista, R. A.; Sandoval, S. B. *Tetrahedron Lett.* **1984**, *25*, 1341–1344; Toyota, M.; Majo, V. J.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 1555–1558.
3. (a) Kende, A. S.; Roth, B.; Sanfilipo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808–5810; (b) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090–2091; (c) Larock, R. C.; Lee, N. H. *Tetrahedron Lett.* **1991**, *32*, 5911–5914; (d) Toyota, M.; Sasaki, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 1193–1195.
4. (a) Toyota, M.; Ihara, M. *Synlett* **2002**, 1211–1222; (b) Toyota, M. *Rev. Heteroat. Chem.* **1999**, *21*, 231–255; (c) Toyota, M.; Rudyanto, M.; Ihara, M. *J. Org. Chem.* **2002**, *67*, 3374–3386.
5. Marvell, E. N.; Whalley, W. *Tetrahedron Lett.* **1970**, 509–512; Holt, D. A. *Tetrahedron Lett.* **1981**, *22*, 2243–2246; Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958–2961; Lange, G. L.; Hall, T.-W. *J. Org. Chem.* **1974**, *39*, 3819–3822.
6. For the preparation of the compound **7**, see: Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35–38; The starting material **8** was prepared by the alkylation of 5-bromovaleric acid with the lithium dianion of 3-butyn-1-ol following the procedure of Ames, D. E.; Covell, A. N.; Goodburn, T. G. *J. Chem. Soc.* **1963**, 5889–5893.
7. The nine-membered lactone **12** was isolated in 46% yield from the hydroxyacid **10** by using the 2-thiopyridyl ester method: Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616. Mukaiyama's procedure was used to prepare the 10-membered lactone **13** (41%): Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50.
8. Silylations of the ketone precursors were typically carried out by adding a solution of the ketone in dry THF to lithium diisopropylamide (1.1 equiv) in dry THF at −78 °C. After stirring 1 h at this temperature, a solution of DMPU (2 equiv) and TBDMSOTf (1.1 equiv) in dry THF was added and the reaction mixture was allowed to

warm to 0 °C. After 1 h, the reaction mixture was quenched with an aqueous saturated solution of sodium bicarbonate, extracted with hexanes, and the organic layer washed with an aqueous saturated solution of sodium bicarbonate and brine. The crude yellow oil was purified by chromatography (silica gel treated with 1% triethylamine in hexanes, 100% hexanes).

9. Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971–5974.
10. Silylations of the macrolactones were carried out with HMPA (1.1 equiv) instead of DMPU. The lithium enolate was trapped with TBDMSCl (1.1 equiv) and slowly warmed to room temperature. After chromatography, the very unstable ketene acetals **5** and **6** were used immediately in the palladium(II) reactions.
11. Cyclizations were typically carried out by addition of a solution of silyl enol ether in acetonitrile/dichloromethane, to a solution of palladium acetate (1.0 equiv) in acetonitrile. After stirring for 16 h under argon at room temperature, the black solution was evaporated to dryness under reduced pressure, diluted with hexanes, and filtered through a plug of Florisil. The filtrate was concentrated, and the resulting yellow oil purified by chromatography (silica gel, gradient hexanes 100%—hexanes–ethyl acetate 9:1).
12. Spectroscopic data (^{1}H, ^{13}C NMR, and MS) of cyclization product **14** were identical to those from an authentic sample obtained during the preparation of the substrate **2**.
13. Spectroscopic data (^{1}H, ^{13}C NMR, IR, and MS) for **15** were in agreement with literature data: Redmond, K.; Carpenter, B. K. *J. Org. Chem.* **1997**, *62*, 5668–5669; Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911–2915.
14. Kende, A. S.; Wustrow, D. J. *Tetrahedron Lett.* **1985**, *26*, 5411–5414.
15. For an alternative mechanistic picture, see Ref. 3c.
16. Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151; Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593–2596, see also Ref. 3c.
17. Spectroscopic data for **19** (^{1}H, ^{13}C NMR, IR, and MS) were in accord with those of an authentic sample independently synthesized according to the following procedures: Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002–2021; Gras, J.-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549–4552.
18. Spectroscopic data (^{1}H, ^{13}C NMR, and IR) for **20** were in agreement with literature data: Jones, J. B.; Dodds, D. R. *Can. J. Chem.* **1987**, *65*, 2397–2404.
19. Spectroscopic data for **21**: ^{1}H NMR ($CDCl_3$): δ 1.85–2.00 (m, 2H), 2.22–2.30 (m, 2H), 4.20–4.25 (m, 2H), 5.45–5.55 (m, 2H), 5.92 (d, 1H, $J = 11$ Hz), 6.41–6.50 (m, 1H). GC/MS (*m*/*e*, 70 eV): $M^+ = 138$ (9%), 121, 110, 91, 80, 79 (100%), 68, 53, 41.
20. Spectroscopic data for **22**: ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 1H), 1.55 (m, 1H), 1.70–1.80 (m, 2H), 1.95 (m, 1H), 2.17 (m, 2H), 2.31 (m, 1H), 2.69 (m, 1H), 3.15 (m, 1H), 5.66 (dd, 1H, $J = 6.1$ Hz), 6.40 (d, 1H, $J = 6.1$ Hz). IR ($CHCl_3$ solution): 2945, 2840–2920, 1740, 1120 cm^{-1}. MS (*m*/*e*, 70 eV): $M^+ = 152$, 124, 109, 95, 83, 81, 69, 68, 67.
21. The chemical shifts and coupling constants of the vinylic protons of **22** as well as the infrared maximum for the carbonyl group were consistent with literature data: Astudillo, L.; Galindo, A.; González, A. G.; Mansilla, H. *Heterocycles* **1993**, *36*, 1075–1080.
22. Ayral-Kaloustian, S.; Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1978**, *43*, 3314–3318.
23. For the preparation of ketone **24**, see: Boeckman, R. K., Jr. *Tetrahedron Lett.* **1977**, 4281–4284.
24. The compound **23** was obtained in two steps from **24**, first by generating the kinetic enolate of **24** with LDA (1.2 equiv) in dry THF and trapping with TMSCl (1.2 equiv), and then by the same oxidative degradation used to transform **22** to **23**, with an overall yield of 39%.