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Palladium-Catalyzed Cyclization of 1,ω-Dienols: Multiple Ways to Intramolecularly Trap a Carbocation

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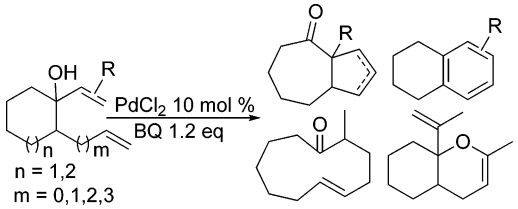
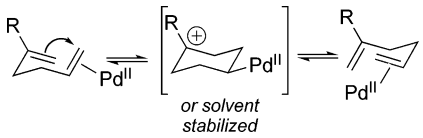


The tandem catalytic cyclization−rearrangement of 1,ω-dien-3-ols by palladium(II) produces different types of products, depending on the structure of starting material. The pinacol rearrangement, benzannulation, and oxy-Cope rearrangement are major pathways of transforming the putative σ-alkylpalladium carbocation. Turnover of the cyclization is achieved by β-hydride elimination and reoxidation of palladium with benzoquinone. The overall course of the reaction is very sensitive to small changes in the substrate structure.

The electrophilic activation of unactivated double bonds by palladium(II) toward *O*-, *N*-, and *C*-nucleophiles constitutes an important class of complexity generating reactions.[1,2] Nucleophilic attack on the palladium−olefin complex results in a new nucleophile−carbon bond and a σ-alkylpalladium complex, which may then participate in additional reactions.[3] In Pd(II)-catalyzed Cope reactions of 1,5-dienes, the nucleophile is another alkene and these processes transiently create carbenium ion character at C5 of a cyclic intermediate (Scheme 1),[4] which subsequently fragments to product and regenerated catalyst.[5]

SCHEME 1



Mechanistic studies additionally implicated antarafacial attack at the Pd-alkene and a chairlike transition structure.[6,7]

Recent efforts in our laboratory have sought to trap this putative cation prior to the fragmentation; an example of intramolecular trapping by a pendant phenol is shown in Scheme 2.[8,9] Catalyst turnover in this instance was achieved by

(1) *Palladium reagents and catalysts*: *new perspectives for the 21st century*; Tsuji, J., Ed.; Wiley: Hoboken, NJ, 2004.

(2) *Transition Metals in the Synthesis of Complex Organic Molecules*; Hegedus, L. S., Ed.; University Science Books: Sausalito, CA, 1999.

(3) For several recent forum articles on this topic see: (a) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903−1909. (b) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910−1923.

(4) (a) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc*. **1980**, *102*, 865−867. (b) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc*. **1982**, *104*, 7225−7231. (c) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579−586. (d) Overman, L. E.; Renaldo, A. F. *J. Am. Chem. Soc*. **1990**, *112*, 3945−3949.

(5) For early cases with stoichiometric quantities of Pd(II), see: (a) Trebellas, J. C.; Olechovski, J. R.; Jonassen, H. B. *J. Organomet. Chem*. **1966**, *6*, 412−420. (b) Heimbach, P.; Molin, M. *J. Organomet. Chem*. **1973**, *49*, 477−482. (c) Heimbach, P.; Molin, M. *J. Organomet. Chem*. **1973**, *49*, 483−494. (d) Brown, E. D.; Sam, T. W.; Sutherland, J.; K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2326−2332. (e) Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc*. **1980**, *102*, 4973−4979.

(6) Electron withdrawing groups can cause nonfragmenting pathways to dominate, see: Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett*. **1983**, *24*, 2235−2238.

(7) For several examples where a nucleophilic alkene (enol, indole, etc.) leads to a cyclic product, see: (a) Widenhoefer, R. A. *Pure Appl. Chem.* **2004**, *76*, 671−678. (b) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250−10251. (c) Toyota, M.; Ihara, M. *Synlett* **2002**, *8*, 1211−1222. (d) Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869−2871. (e) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579.

(8) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405−7410.

(9) Despite how the reaction is shown to proceed in Scheme 2, we suspect that a free carbocation is not likely to form and that the phenol serves to stabilize developing charge. This notion is supported by DFT studies with pincer ligated Pt-dicationic catalysts. See: Nowroozi-Isfahani, T.; Musaev, D. G.; Morokuma, K.; Gagné, M. R. *Organometallics* **2007**, *26*, 2540−2549.

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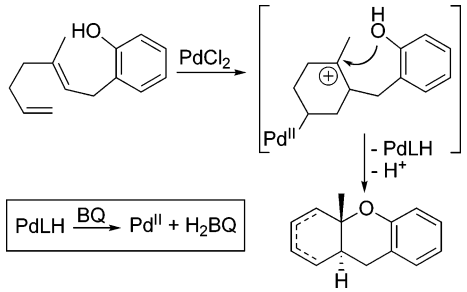
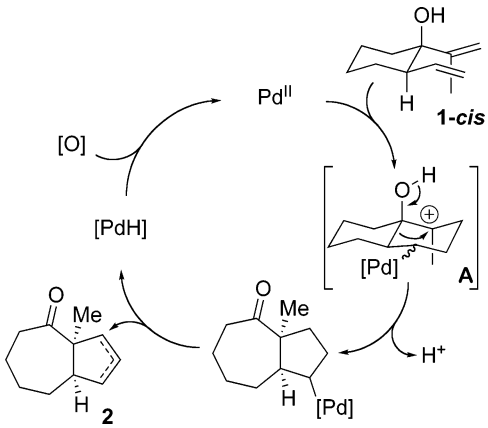
SCHEME 2



SCHEME 3



β-hydrogen elimination and palladium reoxidation with 1,4-benzoquinone (BQ). Key to controlling the point of initiation in these reactions is the strong propensity of Pd(II) and Pt(II) electrophiles to coordinate, and thus activate, the least substituted double bond.[2,8,10] This preference contrasts the behavior of traditional electrophiles (H^+, Br^+, RSe^+, etc).

1,5-Dien-3-ol **1-*cis*** was also examined in the palladium-catalyzed cyclization.[8] The guiding notion in this case was to trap the putative carbocation with a ring-expanding/contracting pinacol rearrangement, in analogy to the Lewis acid initiated processes successfully employed by Overman in natural product synthesis.[11] In the event, the cyclization went as expected and catalyst turnover by β-hydride elimination provided bicyclic ketone **2** as a mixture of regioisomers (Scheme 3). Under oxidizing conditions the resulting "Pd−H" was recycled to the reactive Pd(II) state (BQ proved optimum). The *cis*-fused bicycle ketone was the major product of this reaction, a ring junction that had previously been rationalized by invoking a chairlike topology in the bond migration transition state.[11]

Results and Discussion

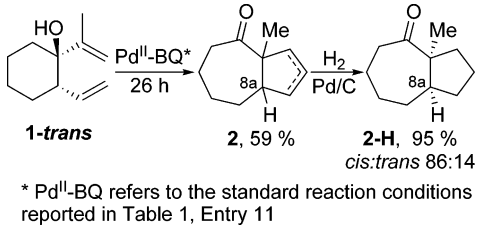
We report herein additional details of scope and efficiency of the palladium-catalyzed cyclization−rearrangement of 1,ω-diene-3-ols. This study was initiated by revisiting the reaction conditions originally reported for the cascade cyclization,[8] paying particular attention to the reoxidation conditions, but also examining palladium source and solvent. The previous conditions utilizing bis(benzonitrile)palladium dichloride ($PdCl_2(PhCN)_2$) in refluxing acetonitrile smoothly converted **1-*cis*** to ketone **2** in 80% yield (Table 1, entry 1). Additional optimization studies revealed that benzoquinone loadings could be reduced to 1.2 equiv, which improved the purification procedure and the yield of **2** (96%, entry 11). As before, **2** was obtained as a mixture of four alkene isomers, which converted to an 80:20 mixture of *cis* and *trans* 3a-methylperhydroazulenones **2-H** upon hydrogenation (H_2, Pd/C).

TABLE 1. Optimization of Reaction Conditions[a]

entry	catalyst (10 mol %)	solvent	cooxidant	time (h)	yield (%)
1	$PdCl_2(PhCN)_2$	MeCN	BQ 1.5 equiv	8	80
2	$PdCl_2(PhCN)_2$	CHCl3	BQ 1.5 equiv	5	54[b,c]
3	$PdCl_2(PhCN)_2$	THF	BQ 1.5 equiv	18	26[b]
4	$PdCl_2(PhCN)_2$ (2 mol %)	MeCN	BQ 1.5 equiv	120	11
5	Pd/C (5 wt %)	MeCN	BQ 1.5 equiv	18	NR
6	$PdCl_2$	MeCN	BQ 1.5 equiv	18	NR
7	$Pd(acac)_2$	MeCN	BQ 1.5 equiv	18	NR
8	$Pd(dba)_2$	MeCN	BQ 1.5 equiv	44	NR
9	$Pd(OAc)_2$	MeCN	BQ 1.5 equiv	21	NR
10	$PdCl_2(PhCN)_2$	MeCN	BQ 4 equiv	6	45
11	$PdCl_2(PhCN)_2$	MeCN	BQ 1.2 equiv	8	96
12	$PdCl_2(PhCN)_2$	MeCN	BQ 1.1 equiv	8	57
13	$PdCl_2(PhCN)_2$	MeCN	BQ 1 equiv	44	65[b]
14	$PdCl_2(PhCN)_2$	MeCN	1,3-dinitro-benzene	27	29[b]
15	$PdCl_2(PhCN)_2$	MeCN	$Cu(OAc)_2$	44	10[b]
16	$PdCl_2(PhCN)_2$	MeCN	$Cu(OAc)_2$ (20%)/O_2	65	very slow reaction[b]

[a] Conditions: 0.05 M in **1**, refluxing in solvent. [b] Determined by GCMS. [c] Multiple byproducts formed.

SCHEME 4



Cyclization of the *trans*-isomer of dienol **1** (**1-*trans***) gave the same bicyclic ketone **2-H** as an 86:14 mixture of isomers (Scheme 4) after hydrogenation. We speculate that our stereochemical leakage comes from the rapid Pd-catalyzed alkene migration, which compromises the C-8a stereo center and is also responsible for the multiple alkene isomers of product.[12]

Reaction Scope

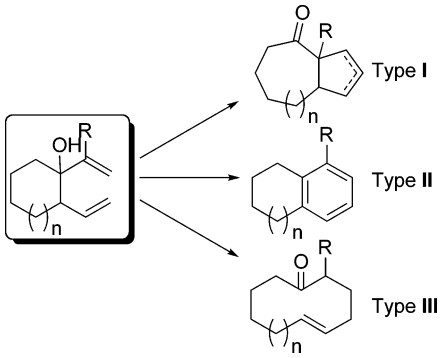
The optimized protocol (Table 1, entry 11) was then applied to a variety of dienols capable of trapping the putative cation via a pinacol rearrangement. In addition to the pinacol reactivity, a priori consideration of alternative reaction pathways predicted multiple routes for transforming the 1,ω-dienols (Schemes 5

(10) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459−3461.

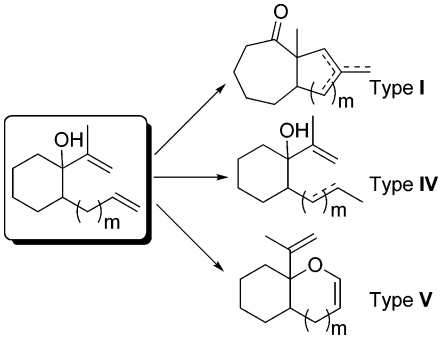
(11) (a) Herrington, P. M.; Hopkins, M. H.; Mishra, P.; Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 3711−3712. (b) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514−1515. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (d) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.*, **1997**, *62*, 6379−6387. (e) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2002**, *67*, 6421−6429. (f) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

(12) We and others have also sought methods that activate alkenes toward nucleophilic attack, but otherwise inhibit β-H elimination as a default method of catalytic turnover. (a) Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038−9039. (b) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013−3015. (c) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379−3381.

SCHEME 5



SCHEME 6



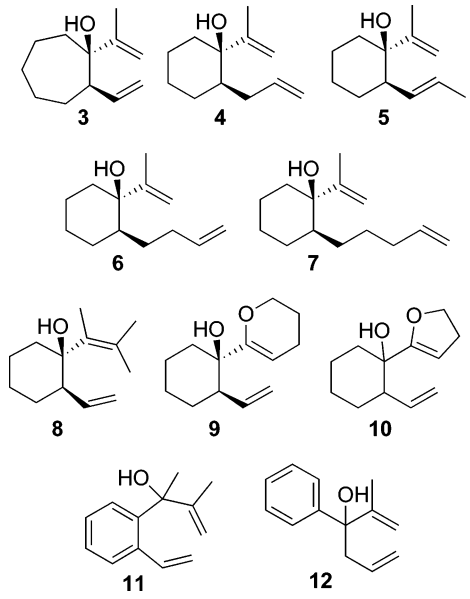
and 6). The desired cyclization manifold is termed Type I, cyclization accompanied by dehydration and aromatization is termed Type II, while the oxy-Cope type pathway is termed Type III. Literature precedence suggested that Type III transformations were entirely reasonable while the Lewis acid reaction conditions suggested the reasonableness of aromatization processes.[13]

For 1,ω-dienols with a longer chain between the double bonds, additional Pd-mediated migration of the double bond to an internal position (Type IV) and Wacker-like nucleophilic attack of the hydroxyl group on the electrophilic palladium−alkene complex (Type V) were also considered (Scheme 6).

A series of substrates were designed to investigate the impact of ring size, distance between the two double bonds, and the effect of steric and electronic perturbations on the mode of cyclization. All the substrates contained the structural features of having a mono- (or 1,2-disubstituted) double bond as the initiation point for complexation by Pd(II), a second nucleophilic alkene for generating a stabilized carbocation,[14] and a tertiary allylic alcohol for initiating the pinacol rearrangement (Scheme 7).

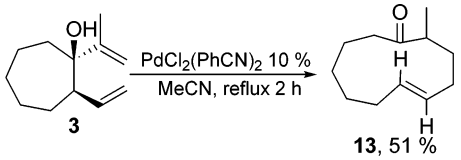
Substrates **3**−**9** were prepared by the *cis*-selective addition of the appropriate organometallic reagent to the 2-substituted cycloalkanones.[15−17] The *cis*-isomers of the 1,2-dialkenylcycloalkanols were a priori considered most favorable since both alkenyl substituents orient equatorially in the cyclization transition state (Schemes 1 and 3). Partially supporting this notion is the lowered yield on cyclizing **1-*trans*** (Scheme 4) instead of

SCHEME 7



1-*cis* (59 vs 96% yield). Compound **10** was prepared as a mixture of *cis*- and *trans*-isomers and was used as is since it was prone to decomposition and isomerization on silica.

Treatment of dienol **3** with catalytic quantities of $PdCl_2(PhCN)_2$ with or without benzoquinone resulted in the formation of *trans*-cycloundecenone **13**, which was characterized by the alkene's large *trans* coupling constant ($^3J_{HH} = 15.2$ Hz) (eq 1).



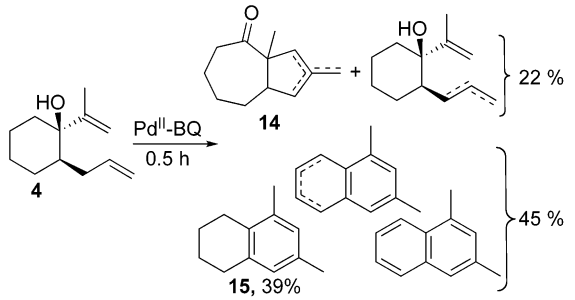
(1)

The analogous transformation was previously described by Malacria and co-workers, who studied the oxy-Cope rearrangement of cyclic and acyclic hexa-1,5-dien-3-ols, initiated either catalytically (Pd(II))[18] or by stoichiometric quantities of $Hg(CF_3COO)_2$.[19] Thermal[17,20] or anionic[21] cyclizations of structurally related 1,2-divinylcyclohexanols similarly generated cyclodecenones. We presume that the course of this reaction is driven by the ring strain in the putative [6.3.0]bicycloundecanone.

In contrast to the parent 1,5-dien-3-ol **1-*cis***, the homologous 1,6-dien-3-ol **4** was considerably more capricious. Under identical reaction conditions total consumption of **4** required only 0.5 h. However, the desired ketone **14**, accompanied by

(13) Grise, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905−5908.
(14) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.
(15) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546.
(16) Holt, D. A. *Tetrahedron Lett.* **1981**, *22*, 2243−2246.
(17) DiMartino, G.; Hursthouse, M. B.; Light, M. E.; Percy, J. M.; Spencer, N. S.; Tolley, M. *Org. Biomol. Chem.* **2003**, *1*, 4423−4434.
(18) Bluthe, N.; Malacria, M.; Gore. J. *Tetrahedron Lett.* **1983**, *24*, 1157−1160.
(19) (a) Bluthe, N.; Malacria, M.; Gore. J. *Tetrahedron Lett.* **1982**, *23*, 4263−4266. (b) Bluthe, N.; Malacria, M.; Gore. J. *Tetrahedron* **1984**, *40*, 3277−3284.
(20) (a) Sworin, M.; Lin, K.-C. *J. Am. Chem. Soc.* **1989**, *111*, 1815−1825. (b) Warrington, J. M.; Yap, G. P. A.; Barriault, L. *Org. Lett.* **2000**, *2*, 663−665. (c) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371−1374. (d) Farand, J. A.; Denissova, I.; Barriault, L. *Heterocycles* **2004**, *62*, 735−748.
(21) (a) Paquette, L. A.; Shi, Y.-J. *J. Am. Chem. Soc.* **1990**, *112*, 8478−8489. (b) Jisheng, L.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426−5428. (c) Chu, Y.; Colclough, D.; Hotchkin, D.; Tuazon, M.; White, J. B. *Tetrahedron* **1997**, *53*, 14235−14246. (d) Chu, Y.; White, J. B.; Duclos, B. A. *Tetrahedron Lett.* **2001**, *42*, 3815−3817. (e) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901−14904.

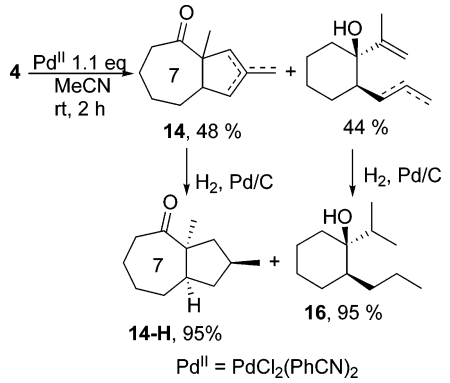
extensive double bond migration, proved to be a minor product (eq 2). Dominant were dehydration/aromatization pathways that presumably proceeded through a similar putative bicyclo[4.4.0]-carbocation **A** (Scheme 3). Dimethyltetraline **15** (39% yield, or 88% of the aromatized products) along with several minor naphthalene-type products (inferred from GC-MS analysis) were obtained (eq 2).



(2)

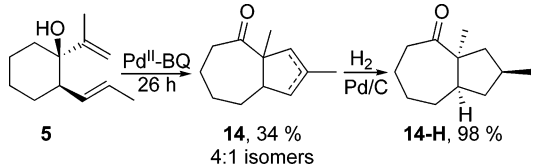
Aromatization could almost be suppressed in stoichiometric reactions of **4** with $PdCl_2(PhCN)_2$ at room temperature (Scheme 8). However, under these conditions along with desired adduct **14**, multiple isomers of starting material were obtained, hydrogenation of which provided a single isomer of 1-isopropyl-2-propylcyclohexanol **16**. Separate hydrogenation of the expected unsaturated ketone **14** (obtained as a mixture of three isomers in the ratio 49:22:18) provided perhydrogenated azulenone **14-H** as single diastereomer. Efforts to modify the reaction conditions and improve the reaction selectivity were unsuccessful.

SCHEME 8

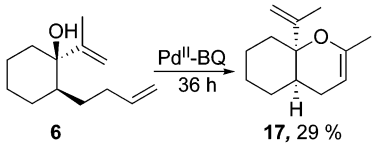


Cyclization of isomeric dienol **5** required more time, but provided the same stereoisomer of ketone **14-H** after hydrogenation (Scheme 9). The strong coordination preference of Pd(II) for monosubstituted alkenes explains the observed 50-fold difference in activity between **4** and **5**.

SCHEME 9



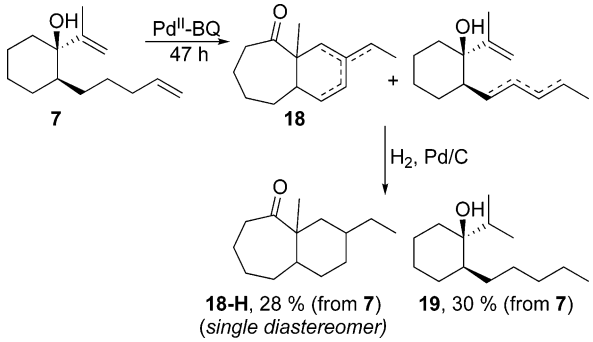
Much longer reaction times (36 h) were required for full conversion of 1,7-dien-3-ol **6**, and instead of the expected bicyclic ketone only hexahydrochromene derivative **17** was isolated (eq 3). This product presumably forms as a result of 6-exo Wacker-type cyclization,[22] followed by alkene migration to the more highly substituted position.



(3)

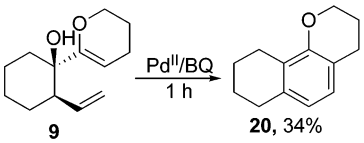
Complete consumption of 1,8-dien-3-ol **7** under standard conditions was similarly slow (47 h), and resulted in an inseparable mixture of two isomers of starting material and four isomers of cycloadduct **18**. Hydrogenation of the mixture provided bicyclic ketone **18-H** as a single diastereomer and dialkylcyclohexanol **19** (Scheme 10). Longer reflux times (168 h) decreased the amount of starting material isomers, but did not increase the yield of **18** (17%). Formation of **18** is only possible if migration of the terminal double bond precedes the cyclization.

SCHEME 10

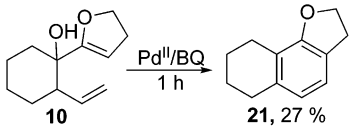


Our attempts to promote the cyclization of dienol **8** were unsuccessful; dehydration and decomposition of starting material were the primarily reaction products observed by GC-MS, with only minor amounts of desired adduct detectable. The tetra-substituted double bond in **8** is apparently too hindered for efficient addition to the electrophilic palladium−alkene complex.

The 1,5-dien-3-ols **9** and **10** contained more nucleophilic trisubstituted double bonds and demonstrated another behavior in the palladium-catalyzed cyclization. These reactions were characterized by rapid rates of starting material consumption and the formation of the aromatic products **20** and **21** (eqs 4 and 5). Attempts to minimize this reaction pathway were unsuccessful. Gold-catalyzed benzannulation of structurally related 3-hydroxy-1,5-enynes was reported recently.[13]



(4)

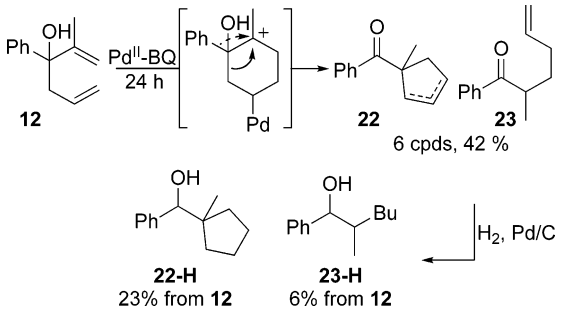


(5)

Although the cyclization of dienol **11** resulted in inseparable dimers and oligomers of starting material, dienol **12** underwent

(22) For a recent review of oxy-palladation of alkenes, see: Muzart, J. *Tetrahedron* **2005**, *61*, 5955−6008.

SCHEME 11



a comparatively smoother reaction. After 24 h the starting material was consumed, and an inseparable mixture of six products (GC-MS) was obtained in 42% yield. Four of these compounds had molecular weights equal to the starting dienol and two had molecular weights indicating net dehydrogenation. Catalytic hydrogenation of this mixture provided **22-H** in the 3.5:1 mixture with alcohol **23-H** (obtained as a mixture of two diastereomers by NMR). Formation of cyclic adduct **22-H** confirmed that ring contractive alkyl migration in a putative monocyclic cation can indeed occur (Scheme 11), while formation of **23** indicates that oxy-Cope-type rearrangements can be competitive.[23] Unfortunately, the complex nature of the reaction mixture makes additional comments on competing arene transfer suspect.

We report herein our investigation of the palladium-catalyzed cyclization of compounds containing the 1,ω-diene-3-ol structural motif. Depending on the structural features of the substrates, numerous cyclization and/or rearrangement pathways are possible. Formation of the products of pinacol rearrangement (Type I), benzannulation (Type II), and oxy-Cope rearrangement (Type III) are together supportive of the formation of intermediate carbocation **A** (Scheme 1). Other possible Pd-catalyzed transformations included Wacker-type cyclization (Type V) and precyclization migration of the double bond (Type IV). Turnover of the cyclizations is achieved by β-hydride elimination and reoxidation of palladium with benzoquinone.

(23) Hydrogenation of unsaturated ketones **22** and **23** proceeds with carbonyl reduction, see: (a) Sajiki, H.; Hattori, K.; Hirota, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043−4044. (b) Mori, A.; Mizusaki, T.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2006**, *62*, 11925−11932 and references cited therein.

Experimental Section

General Procedure for Catalytic Cyclization and Hydrogenation of Products. Palladium-catalyzed cyclization reactions were performed under an argon atmosphere with use of standard Schlenk techniques. To a solution of dienol **1** (166 mg, 1 mmol) and *p*-benzoquinone (129.6 mg, 1.2 mmol) in dry acetonitrile (20 mL) was added $PdCl_2(PhCN)_2$ (38.3 mg, 0.1 mmol). The resulting solution was stirred at 80 °C for 8 h and monitored by GCMS. After complete consumption of starting material the reaction mixture was cooled to room temperature, concentrated under vacuum, and chromatographed (hexanes−EtOAc 9:1) to give a mixture of bicyclic products **2** (157 mg, 96%) as a colorless oil. The oil was taken up in MeOH (10 mL), and Pd/C (5 mol %) was added. The resulting suspension was stirred under hydrogen atmosphere (1 atm) at room temperature for 4 h. The reaction mixture was filtered through a plug of Celite and washed with ether. The filtrate was concentrated under vacuum to give a colorless oil of bicyclic ketone **2-H** (151 mg, 95%) as an 80:20 mixture of adducts.

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Supporting Information Available: Detailed experimental procedures, synthesis of the substrates, streochemistry proof, NMR spectra, and characterization data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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