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Palladium(II)-Catalyzed Cycloisomerization of Functionalized 1,5-Hexadienes

Björn Nelson, Wolf Hiller, Annett Pollex, and Martin Hiersemann*

Fakultät Chemie, Technische Universität Dortmund, 44227 Dortmund, Germany

martin.hiersemann@udo.edu

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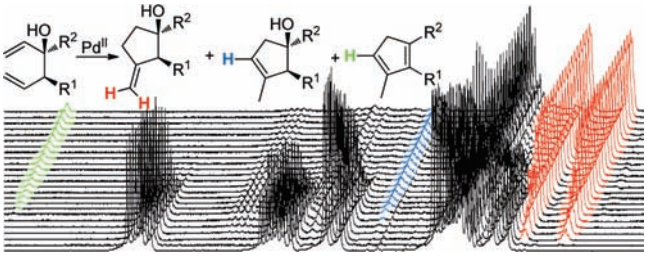
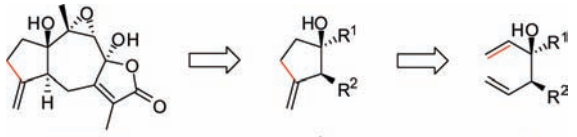
ABSTRACT



Scope and limitations of the Pd(II)-catalyzed cycloisomerization of functionalized 1,5-hexadienes have been studied. In situ NMR experiments indicate a challenging competition between various reaction pathways. A careful balance between substrate structure, nature of the precatalyst, and reaction conditions was required to gain access to a useful building block for sesquiterpene total synthesis.

Provoked by our efforts toward the total synthesis of the marine 8,12-guaianolide menverin F,[1] we seek access to highly substituted methylene cyclopentane building blocks **1** (Scheme 1).

Scheme 1



An intuitive and atom economic retrosynthetic strategy rests on a cycloisomerization transform to provide functionalized 1,5-hexadiene synthons **2**. Unfortunately, and in stark contrast to the metal-catalyzed cycloisomerization of 1,6-heptadienes, which has been thoroughly investigated,[2] only a limited number of examples exists for the cycloisomerization of 1,5-hexadienes to functionalized methylene cyclopentanes.[3] As exemplified in Scheme 2, particularly relevant to our endeavor are the results of Livinghouse,[4] Widenhoefer,[5] and Lloyd-Jones.[6] Notably, the known Pd(II)-based procedures trigger double bond isomerization and, thereby, convert the initially formed methylene cyclopentanes into methyl cyclopentenes. Nonetheless, and in light of potential chemoselectivity issues with highly functionalized substrates, we elected to pursue the Pd(II)-catalyzed cycloisomerization, and for that purpose, the known 1,5-hexadiene **2a**[7] was used for the initial search of catalysts and conditions which would support methylene cyclopentane formation (Table 1).

(1) Li, L.; Wang, C.-Y.; Huang, H.; Mollo, E.; Cimino, G.; Guo, Y.-W. *Helv. Chim. Acta* **2008**, *91*, 111–117.

(2) For selected reviews, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (b) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905–913. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215–236.

(3) For early transition-metal-catalyzed cycloisomerizations of unfunctionalized 1,5-hexadienes, see: (a) Mach, K.; Sedmera, P.; Petrusova, L.; Antropiusova, H.; Hanus, V.; Turecek, F. *Tetrahedron Lett.* **1982**, *23*, 1105–1108. (b) Lehmkuhl, H.; Tsien, Y.-L. *Chem. Ber.* **1983**, *116*, 2437–2446. (c) Akita, M.; Yasuda, H.; Nagasuna, K.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 554–558. (d) Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett* **1990**, 74–84. (e) Bazan, G. C.; Rodriguez, G.; Ashe, A. J.; Al-Ahmad, S.; Kampf, J. W. *Organometallics* **1997**, *16*, 2492–2494. (f) Thiele, S.; Erker, G. *Chem. Ber.* **1997**, *130*, 201–207.

(4) Okamoto, S.; Livinghouse, T. *Organometallics* **2000**, *19*, 1449–1451.

(5) Kisanga, P.; Goj, L. A.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 635–637.

(6) Bray, K. L.; Lloyd-Jones, G. C.; Munoz, M. P.; Slatford, P. A.; Tan, E. H. P.; Tyler-Mahon, A. R.; Worthington, P. A. *Chem.—Eur. J.* **2006**, *12*, 8650–8663.

(7) Hiersemann, M. *Synlett* **2000**, 415–417.

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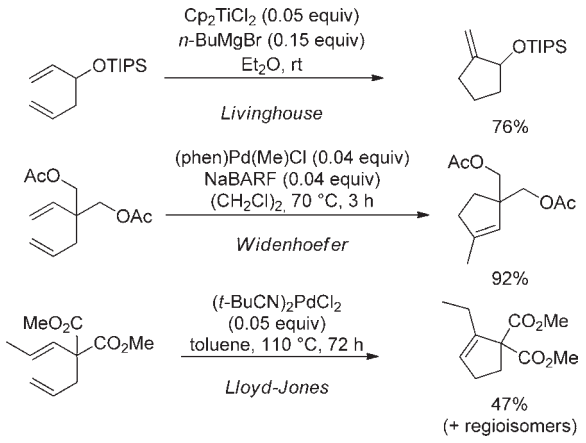
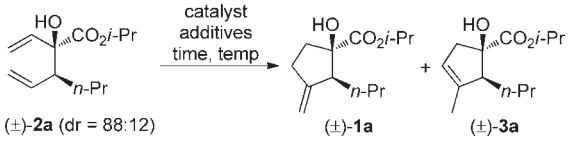
Scheme 2



On the basis of pratical considerations, we decided to commence our study by using the readily available, bench-stable $(MeCN)_2PdCl_2$ as precatalyst. However, initial experiments in CH_2Cl_2 afforded only recovered starting diene **2a**, even at elevated temperatures (entry 1). Performing the same experiment in toluene at reflux indeed triggered cycloisomerization, in accordance with the literature (vide supra), in favor of the undesired methyl cyclopentene **3a** (entry 2). Considering Widenhoefer's results, we next prepared more electrophilic Pd(II) complexes by counterion metathesis. Treatment of $(MeCN)_2PdCl_2$ with $AgSbF_6$ or AgOTf indeed led to an active precatalyst which provided small amounts of the cycloisomerization product, albeit in favor of the undesired **3a** (entries 3 and 4). The first significant progress was achieved when $AgBF_4$ was utilized for chloride metathesis; in the event, the desired cycloisomerization product was isolated in moderate yield (40%), but with an encouraging preference (**1a**:**3a** = 95:5) for methylene cyclopentane formation (entry 5). A comparable result (48%, **1a**:**3a** = 89:11) was obtained with the commercially available $[Pd(MeCN)_4](BF_4)_2$[8] (entry 6). $[Pd(allyl)(MeCN)](BF_4)$ was found to be less active then $[Pd(MeCN)_4](BF_4)_2$ and, when employed at increased reaction temperature, fostered the formation of the undesired methyl cyclopentene (entries 7 and 8).

Relying on the $[Pd(MeCN)_4](BF_4)_2$ precatalyst, we next attempted to adjust the catalytic activity by adding different phosphines. Significantly, in the event of adding 2 equiv of (*c*-hexyl)$_3$P, no cycloisomerization products were obtained (entry 9). Addition of equimolar amounts of (*c*-hexyl)$_3$P, (*t*-Bu)$_3$P, (*c*-pentyl)$_3$P, or (*i*-Pr)$_3$P provided an active catalyst system (entries 10−13); however, reactivity and chemoselectivity were markedly dependent on the nature of the phosphine and generally inferior compared to experiments performed in the absence of phosphine additives. We continued our screening by deploying Pd(II) precatalysts containing bidentate chelating ligands. Accordingly, in situ chloride abstraction from (2,2′-bipy)$PdCl_2$

Table 1. Screening of Catalysts and Conditions for the Cycloisomerization of **2a**[a]



entry	catalyst, additives (equiv)	temp (°C)	time (h)	yield[b] (%) (**1a**:**3a**)[c]
1	$(MeCN)_2PdCl_2$ (0.05)	60	19	no reaction
2	$(MeCN)_2PdCl_2$ (0.05)	110	19	50[d] (0:100)
3	$(MeCN)_2PdCl_2$ (0.05), $AgSbF_6$ (0.1)	rt	2	10 (5:95)
4	$(MeCN)_2PdCl_2$ (0.05), AgOTf (0.1)	rt	2	7 (14:86)
5	$(MeCN)_2PdCl_2$ (0.05), $AgBF_4$ (0.1)	rt	2	40 (95:5)
6	$[Pd(MeCN)_4](BF_4)_2$ (0.05)	rt	2	48 (89:11)
7	$[Pd(allyl)(MeCN)_2](BF_4)$ (0.05)	rt	72	40[e] (95:5)
8	$[Pd(allyl)(MeCN)_2](BF_4)$ (0.05)	60[f]	19	49 (69:31)
9	$[Pd(MeCN)_4](BF_4)_2$ (0.05), P(*c*-hexyl)$_3$ (0.1)	60	19	no reaction
10	$[Pd(MeCN)_4](BF_4)_2$ (0.05), P(*c*-hexyl)$_3$ (0.05)	rt	19	48 (85:15)
11	$[Pd(MeCN)_4](BF_4)_2$ (0.05), P(*t*-Bu)$_3$ (0.05)	rt	19	complex mixture
12	$[Pd(MeCN)_4](BF_4)_2$ (0.05), P(*c*-pentyl)$_3$ (0.05)	rt	19	28 (68:32)
13	$[Pd(MeCN)_4](BF_4)_2$ (0.05), P(*i*-Pr)$_3$ (0.05)	rt	19	48 (72:28)
14	(2,2′-bipy)$PdCl_2$ (0.05), $AgBF_4$ (0.1)	60	19	39 (5:95)
15	(dppe)$PdCl_2$ (0.05), $AgBF_4$ (0.1)	60	19	no react
16	$Pd(dba)_2$ (0.05), $HBF_4 \cdot Et_2O$ (0.05)	rt	90	30 (58:42)

[a] Experiments conducted with 0.4 mmol **2a** in CH_2Cl_2 (c = 0.1 M). Reactions at elevated temperatures were run in a sealed tube. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy of the purified product. [d] Solvent: toluene; yield determined by ^{1}H NMR spectroscopy. [e] **2a** (20%) recovered. [f] Solvent: $(CH_2Cl)_2$; dppe = 1,2-bis(diphenylphosphino)ethane; 2,2′-bipy = 2,2′-bipyridyl; dba = dibenzylideneacetone.

with $AgBF_4$ provided a precatalyst that catalyzed the cycloisomerization at elevated temperature (39%, **1a**:**3a** = 5:95), however, in favor of the formation of the undesired **3a** (entry 14). The Pd(II) complex generated from (dppe)-$PdCl_2$ and $AgBF_4$ was not competent to catalyze the desired cycloisomerization (entry 15). Finally, and assuming a hydrido palladium(II) species as actual catalyst,[2,6] $Pd(dba)_2$ and HBF_4 were pooled with the intent of preparing a L_nPdH complex (entry 15);[9] in the event, cycloisomerization was indeed observed but with an insignificant selectivity in favor for **3a** (30%, **1a**:**3a** = 58:42).

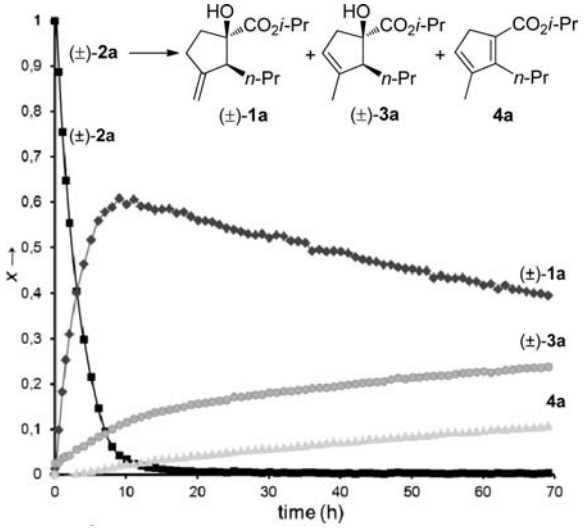
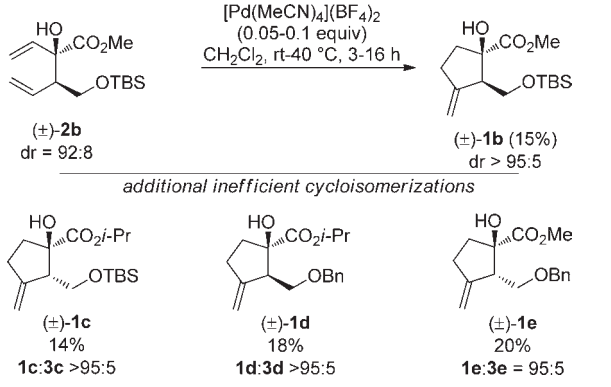


Figure 1. ^1H NMR kinetic profile for the cycloisomerization of (±)-**2a** with $[Pd(MeCN)_4](BF_4)_2$ (0.05 equiv). Experiments were performed using a Shigemi NMR tube in $CDCl_3$ (c = 0.1 M) at 27 °C.

We next studied the course of the cycloisomerization of diastereomerically pure **2a** with $[Pd(MeCN)_4](BF_4)_2$ in $CDCl_3$ by ^1H NMR spectroscopy (Figure 1). The kinetic profile nicely illustrates the consumption of the starting diene with concomitant formation of the desired methylene cyclopentane **1a**.[10] The result emphasizes the impact of reaction duration on yield and selectivity because initially formed **1a** is slowly but steadily consumed and converted to the undesired methyl cyclopentene **3a** and, by subsequent elimination, to the cyclopentadiene **4a**.[11]

Having identified a manageable and effective catalyst, we set out to adapt the structure of the hexadiene substrate to the requirements of our retrosynthesis (Scheme 1). Therefore, the siloxy-substituted hexadiene **2b** was synthesized and treated with $[Pd(MeCN)_4](BF_4)_2$ in CH_2Cl_2 (Scheme 3). Disappointingly, however, even after varying catalyst loading, temperature profile, reaction time, protecting group, and relative configuration of the substrates **2b**–**e**, the cycloisomerization process was largely inefficient in providing synthetically useful yields of the desired methylene cyclopentanes **1b**–**e**.

Scheme 3



In light of this disappointing result, we opted for the introduction of a silyl group as a synthetic equivalent for the hydroxyl group (Scheme 4). Accordingly, the allylic alcohol **5**[12] was converted to the allyloxy actetate **6** by etherification and esterification; a subsequent aldol condensation then delivered the allyl vinyl ether **7**.[13,14] Upon treatment with LDA, **7** is converted to the corresponding ester dienolate which undergoes a moderately diastereoselective [2,3]-Wittig rearrangement to afford the 1,5-hexadiene **2f** in very good yield (89%, *syn*:*anti* = 86:14).[15] The mixture of diastereomers of **2f** was used for the subsequent cycloisomerization reaction which, compared to the cycloisomerization of **2a** (vide supra), required elevated reaction temperatures and an increased reaction time. In the event, we were delighted to obtain the desired methylene cyclopentane *cis*-**1f** in up to 58% yield;[16] additionally, small amounts of *trans*-**1f** and **3f** were detected and isolated as an inseparable mixture. Disappointingly, subsequent

(8) Schramm, R. F.; Wayland, B. B. *Chem. Commun.* **1968**, 898–899. In our hands, different commercial and self-synthetized batches of $[Pd(MeCN)_4](BF_4)_2$ exerted a discrete phenotype and reactivity (see Supporting Information).

(9) For a review on the chemistry of hydrido complexes of palladium, see: Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011–2034.

(10) Notably, the rate of conversion is significantly slower under the conditions of the NMR experiment.

(11) The incomplete mass balance is due to the formation of dimers by Heck reaction of the Pd-σ-complex that emerges from the hydropalladation/intramolecular carbopalladation sequence. Details will be published in a full paper.

(12) Le Menez, P.; Fargeas, V.; Berque, I.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592–3599.

(13) Hiersemann, M. *Synthesis* **2000**, 1279–1290.

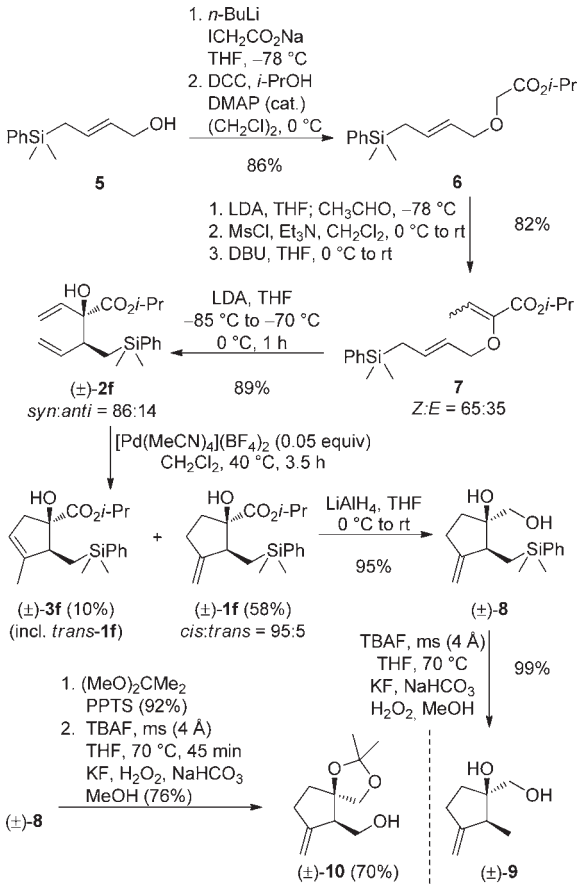
(14) **2f** is prone to undergo a Gosteli–Claisen rearrangement if stored at ambient temperature. Apparently, the comparatively low barrier for the rearrangement of **2f** is caused by a remarkable rate-accelerating effect of the $PhMe_2SiCH_2$ substituent. See: (a) Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531–1540. (b) Rehbein, J.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 4336–4342.

(15) The relative configuration of the major diastereomer *syn*-**2f** was expected based on the proposed stereochemical model for ester dienolate [2,3]-Wittig rearrangements. See: (a) Hiersemann, M. *Tetrahedron* **1999**, *55*, 2625–2638. (b) Hiersemann, M.; Lauterbach, C.; Pollex, A. *Eur. J. Org. Chem.* **1999**, 2713–2724. (c) Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* **2003**, 1088–1095. Later corroborated by X-ray crystallography. See: Nelson, B.; Schürmann, M.; Preut, H.; Hiersemann, M. *Acta Crystallogr.* **2010**, *E66*, o3102.

(16) The assignment of the relative configuration of *cis*-**1f** is supported by NOE experiments. See the Supporting Information for details.

attempts to materialize the synthetic equivalency between the $PhMe_2Si$ and the hydroxyl group by Tamao–Flemming oxidation[17] of **1f** under various conditions [$Hg(OAc)_2$, CH_3CO_3H;[18] $BF_3 \cdot 2AcOH$, H_2O_2, or *m*CPBA, KF;[17b,c] TBAF, KF, H_2O_2;[19] KH, *t*-BuOOH, TBAF[20]] led mainly to decomposition.

Scheme 4



In an alternative approach, the ester **1f** was treated with LAH to deliver the diol **8**, which was exposed to TBAF in the presence of molecular sieves (ms) and, subsequently, subjected to a Tamao oxidation to deliver, perhaps surprisingly,[21] the undesired protodesilylation product **9**. We suspected a critical role of the hydroxyl groups in **8** for the formation of **9**; thus, the diol was capped by acetalization, and subsequent oxidation then afforded the desired building block **10**.

Having accomplished the synthesis of the building block **10** by an unprecedented rearrangement/cycloisomerization sequence, we set out to probe the scope of the cycloisomerization chemistry a little further. Accordingly, structurally modified 1,5-hexadienes (**8**, **2g**–**l**) were synthesized[22] and subjected to the previously optimized conditions (Figure 2). Unfortunately, none of the implemented structural variations resulted in an improved reactivity or selectivity. Whereas acetylation of the tertiary hydroxyl group (**1g**) or the presence of a Weinreb amide (**1j**) is tolerated, the presence of a 1,2-diol (**8**), even if partially (**1i**) or fully protected (**1k**), caused rate deceleration and/or deteriorated chemoselectivity; the oxirane **2l** decomposed under the reaction conditions.

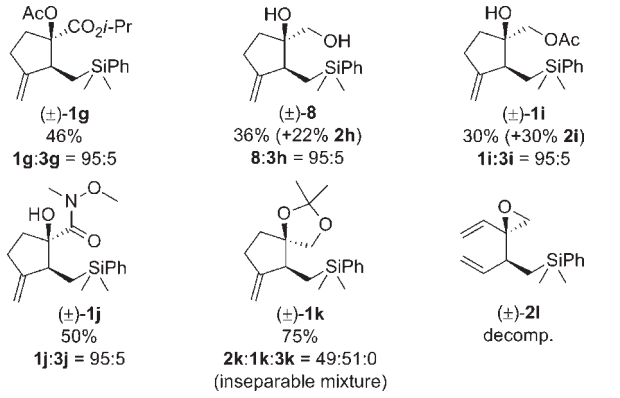


Figure 2. Conditions: **2g**–**l**, $[Pd(MeCN)_4](BF_4)_2$ (0.05 equiv), CH_2Cl_2, 19 h, rt (**2g**,**i**,**j**) or 40 °C (**2h**,**k**).

On the basis of a straightforward retrosynthetic approach for the marine 8,12-guaianolide menverin F, efforts were initiated to extend the current scope of the Pd(II)-catalyzed diene cycloisomerization chemistry; initial results now demonstrate that careful choices of substrate structure and conditions are cornerstones to a moderately successful cycloisomerization of 1,5-hexadienes to provide methylene cyclopentanes. Additional efforts aimed at a mechanism-based rational improvement of the catalyst system are desirable in order to further adapt the capabilities of the catalyst to the synthetic challenge imposed by our retrosynthesis.

Acknowledgment. Financial support by the DFG (HI 628/10-1) and the Technische Universität Dortmund is gratefully acknowledged.

Supporting Information Available. Experimental procedures, spectral and analytical data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For experimental procedures and characterization, see the Supporting Information.