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Palladium Hydroxide Catalyzed Isomerization of Primary Allylic Alcohols to Aldehydes: Application to the Formal Synthesis of (−)-Brevisamide

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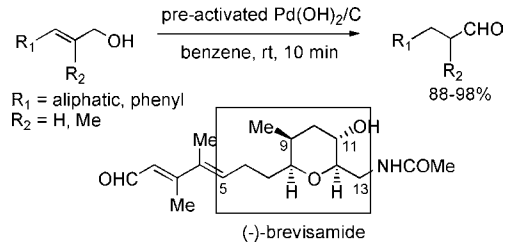
ABSTRACT



The Pd-catalyzed isomerization of primary allylic alcohols into the corresponding saturated aldehydes has been achieved at room temperature for the first time in good to excellent yields under mild conditions. The functional group compatibility in this reaction is studied, and this new methodology has been successfully applied in the synthesis of a C5−C13 tetrahydropyran ring system of (−)-brevisamide in seven steps.

Palladium-catalyzed transformations are of great importance in modern synthetic organic chemistry since they tolerate many functional groups. The value of these reactions can be greatly enhanced by combining two or more Pd-catalyzed transformations either in a successive way or as a domino process.[1] Clearly, the latter approach not only is more efficient and elegant but also has environmental and economical advantages. Aldehydes are versatile synthetic intermediates for various pharmaceuticals, agrochemicals, and other fine chemicals.[2] The conversion of allylic alcohols to the corresponding saturated aldehydes or ketones is a synthetic process which usually requires a two-step sequence of oxidation and reduction reactions. A one-pot catalytic transformation equivalent to an internal redox process is an attractive strategy and a completely atom- economical process that offers several useful applications in natural-product syntheses and in bulk chemical processes. Several transition metal catalysts[3] have been utilized to effect the isomerization reaction of allylic alcohols. In many cases the isomerization

(1) For reviews, see: (a) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley: Hoboken, NJ, 2002. (c) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, Vols. 1 and 2; Wiley-VCH: Weinheim, 1998. (d) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH, Weinheim, 1998; pp 99−166. (e) *Handbook of Palladium-Catalyzed Organic Reactions*; Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y., Eds.; Academic Press: London, 1997.

(2) (a) *Organic Syntheses via Metal Carbonyls*; Wender, I., Pino, P., Eds.; Wiley: New York, 1977. (b) *New Syntheses with Carbon Monoxide*; Falbe, J., Eds.; Springer: Berlin, 1980; pp 1−225. (c) Kohlpaintner, C. W.; Frohning, C. D. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, pp 1−39.

(3) For recent reviews, see: (a) Van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1–24. (b) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27–52. (c) Cadierno, V.; Crochet, P.; Gimeno, J. *Synlett* **2008**, 1105–1124. (c) For relevant examples, see: (d) Markó, I. E.; Gautier, A.; Tsukazaki, M.; Llobet, A.; Plantalech-Mir, E.; Urch, C. J.; Brown, S. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1960–1962. (e) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870–9871. (f) Martin-Matute, B.; Boga'r, K.; Edin, M.; Kaynak, F. B.; Bäckvall, J. E. *Chem.—Eur. J.* **2005**, *11*, 5832–5842. (g) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Varela-Álvarez, A.; Sordo, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 1360–1370. (h) Reetz, M. T.; Hougchao, G. *Synlett* **2006**, 2127–2129. (i) Mantilli, L.; Mazet, C. *Tetrahedron Lett.* **2009**, *50*, 4141–4144.

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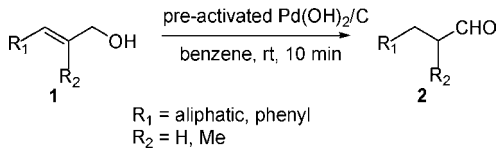
requires relatively high quantities of catalysts. This coupled with rather harsh reaction conditions and the use of expensive metals (for instance Rh,[3e] Ir[3i])[3a,b] has limited the use of most of them in this transformation. More importantly, the issue of functional group compatibility in this reaction has not been addressed. To the best of our knowledge, there is one literature precedent[4a] at elevated temperatures for the isomerization of (*Z*)-but-2-en-1,4-diol to 4-hydroxy butyraldehyde using various Pd catalysts. Similarly, one example with hydrogen preactivated Pd/C is known; this was recognized in the gas phase[4b,c] using a flow apparatus (~180 °C).

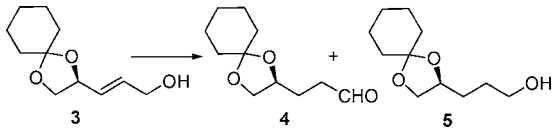
Herein, we describe the first catalytic isomerization of primary allylic alcohols to the corresponding saturated aldehydes using hydrogen preactivted Pd catalysts (Scheme 1), and we demonstrate the application of this protocol in a concise synthesis of a C5−C13 tetrahydropyran ring system of (−)-brevisamide.

Scheme 1. Isomerization of Primary Allylic Alcohols



The isomerization of allyl alcohol **3** (Table 1) was first carried out in EtOAc with hydrogen preactivated (for 30 min) Pd/C at room temperature to furnish saturated aldehyde **4** in 69% yield along with 17% of saturated alcohol **5** within 25 min. The yield of the product was determined after isolating the pure product by column chromatography.

Table 1. Optimization of the Reaction Conditions[a]

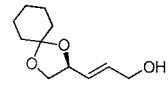
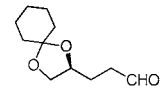
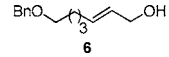
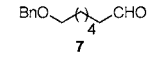
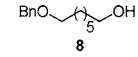
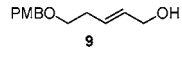
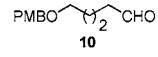
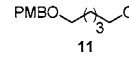
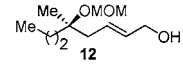
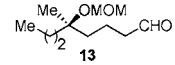
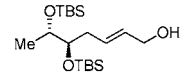
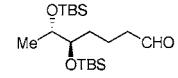
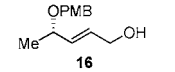
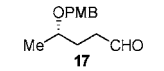
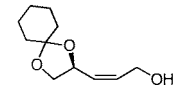
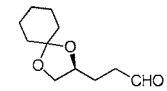
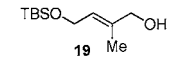
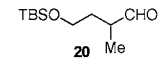
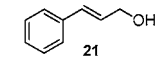
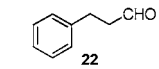
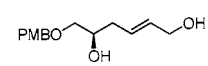
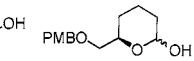


				isolated yield (%)	
entry	catalyst	solvent	*t* (min)	**4**	**5**
1[b]	Pd/C	EtOAc	25	69	17
2[b]	Pd/C	benzene	20	79	9
3[b]	Pd/C	MeOH	30	59	25
4[b]	$Pd(OH)_2$	toluene	10	92	–
5[b]	$Pd(OH)_2$	benzene	10	98	–
6[c]	Pd/C	benzene	60	–	–
7[c]	$Pd(OH)_2$	benzene	60	–	–

[a] Reactions carried out at 100 mg scale. [b] H_2-preactivated catalyst was used. [c] Catalyst was used without activation.

To optimize the reaction conditions, several parameters were varied, including solvent, different Pd catalysts, and the reaction concentration. The reaction was performed in various solvent systems such as EtOAc, benzene, toluene, and methanol at room temperature with hydrogen preactivated 10% Pd/C. Benzene was found to be superior to other solvents in terms of product yield. From Table 1, it is evident that $Pd(OH)_2$ proved to be more effective than Pd/C as a catalyst both in reaction time and yield. Moreover the reaction was found to be very clean with $Pd(OH)_2$, and no byproduct was detected. The scope of the isomerization reaction of **9** (Table 2) was studied using a variable concentration of $Pd(OH)_2$ catalyst. A loading of 12 mol % of catalyst resulted in a 6.5:3.5 ratio of aldehyde to alcohol, while, with 3 mol % of catalyst, no reaction was observed. The ratio of aldehyde to alcohol was increased to 8.5:1.5 by using 7 mol % of catalyst. 20% $Pd(OH)_2$ over charcoal in benzene that had been activated for about 30 min at room temperature under a hydrogen atmosphere. The addition of allyl alcohol **3** in benzene to freshly activated $Pd(OH)_2$ in

Table 2. H_2-Preactivated $Pd(OH)_2$[a,b] Catalyzed Isomerization of Primary Allylic Alcohols

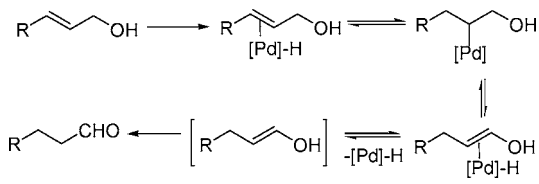
allylic alcohol	Product aldehyde	Product alcohol	Total yield (%)	Ratio[c]
 **3**	 **4**	---	98	10:0
 **6**	 **7**	 **8**	95	9:1
 **9**	 **10**	 **11**	94	8.5:1.5
 **12**	 **13**	---	90	10:0
 **14**	 **15**	---	95	10:0
 **16**	 **17**	---	96	10:0
 **18**	 **4**	---	98	10:0
 **19**	 **20**	---	94	10:0
 **21**	 **22**	---	92	10:0
 **23**	 **24**	---	88	10:0

[a] Reactions carried out for 10 min at room temperature with H_2-preactivated 20% $Pd(OH)_2$/C. [b] 7 mol % catalyst was used. [c] Product ratio (aldehyde:alcohol) was determined after purification by column chromatography. [d] 5 mol % of Et_3N was used.

(4) (a) Sedding, B.; Alm, J. *J. Prakt. Chem. Band* **1987**, *329*, 711–716. (b) Delaby, R. *Compt. Rend.* **1926**, *182*, 140–142. (c) Kraus, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 460–465.

benzene resulted exclusively in the formation of aldehyde **4** within 10 min. When a similar reaction was performed with a continuous H_2-supply using a H_2-balloon, the reaction yielded both aldehyde **4** and saturated alcohol **5** in a 3:2 ratio. Use of base (NEt_3 or Na_2CO_3) was necessary to prevent deprotection[5] of Bn, PMB, and TBS groups present in the substrate. However, no reaction was observed using Pd/C or $Pd(OH)_2$ without activation using H_2-gas. A plausible mechanism is illustrated in Scheme 2.[3g]

Scheme 2. Plausible Mechanism for the Isomerization of Allylic Alcohols



To illustrate the scope of the new protocol, the optimized conditions were applied to a wide variety of substrates bearing different sensitive functional groups such as MOM, Bn, PMB, and TBS ethers. All of these survived the reaction conditions, producing the desired saturated aldehydes in good to excellent yield. The results are outlined in Table 2. Cinnamyl alcohol **21** (Table 2) was readily isomerized to 3-phenylpropanal **22** in 92% yield. In the literature, 3-arylpropanals are usually obtained indirectly by rather sophisticated and tedious procedures (e.g., by the reduction of *trans*-cinnamaldehyde[6] or 3-phenylpropionyl chloride or its derivatives[7] or by the oxidation of 3-arylpropanol[8] or the hydroformylation of styrene[9]), which inhibit its widespread usage. Our method is more effective even in the case of trisubstituted allyl alcohol **19**. In the case of a substrate containing a free hydroxy group as in **23**, a tandem isomerization/cyclization process in one step afforded the corresponding lactol **24** as the sole product in 88% yield. Whereas, Chickos *et. al*[10] observed formation of saturated 1,4-butane diol along with 2-hydroxytetrahydrofuran during the hydrogenation of 1,4-butyne diol using Pd catalysts.

(5) Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. H. *Org. Lett.* **2006**, *8*, 3279–3281.

(6) (a) Terstiege, I.; Maleczka, R. E. *J. Org. Chem.* **1999**, *64*, 342–343. (b) Guin, D.; Baruwati, B.; Manorama, S. V. *Org. Lett.* **2007**, *9*, 1419–1421.

(7) For 3-phenylpropionyl chloride: (a) Jia, X.; Liu, X.; Li, J.; Zhao, P.; Zhang, Y. *Tetrahedron Lett.* **2007**, *48*, 971–974. (b) Maeda, H.; Maki, T.; Ohmori, H. *Tetrahedron Lett.* **1995**, *36*, 2247–2250. (b) For 3-phenylpropionyl acid: (c) Goossen, L. J.; Ghosh, K. *Chem. Commun.* **2002**, 836–837. (d) Uchiyama, M.; Furumoto, S.; Saito, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11425–11433. (d) For 3-phenylpropionyl amide: (e) Shono, T.; Masuda, H.; Murase, H.; Shimomura, M.; Kashimura, S. *J. Org. Chem.* **1992**, *57*, 1061–1063. (f) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408–3419.

(8) (a) Karimi, B.; Abedi, S.; Clark, J. H.; Budarin, V. *Angew. Chem.* **2006**, *118*, 4894–4897. (b) Karimi, B.; Abedi, S.; Clark, J. H.; Budarin, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 4776–4779. (c) Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.* **2001**, *123*, 7449–7450. (d) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

(9) Yu, S.; Chie, Y.-m.; Guan, Z.-h.; Zou, Y.; Li, W.; Zhang, X. *Org. Lett.* **2009**, *11*, 241–244.

(10) Chickos, J. S.; Uang, J. Y.-J. *J. Org. Chem.* **1991**, *56*, 2594–2596.

Our methodology was applied to the synthesis of the C5−C13 tetrahydropyran core unit **35** of (−)-brevisamide (**25**) (Figure 1). Marine polycyclic ethers have attracted the

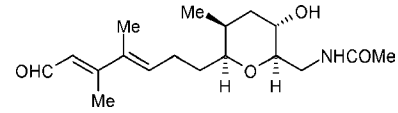
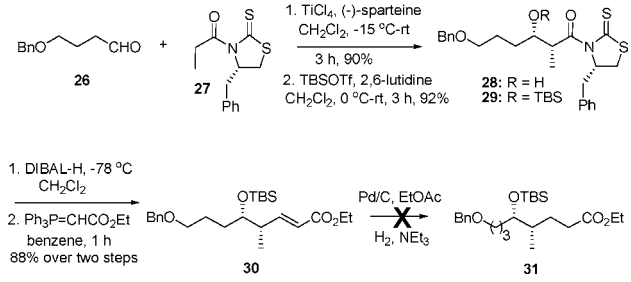


Figure 1. (−)-Brevisamide (**25**).

attention of numerous synthetic organic chemists due to their unique structures and potent bioactivities. Recently, Wright and co-workers have reported the isolation and characterization of brevisamide (**25**), a new marine cyclic ether alkaloid, from cultures of *Karenia brevis*.[11] The structure consists of a single tetrahydropyran ring with 3β-methyl and 5α-hydroxyl groups, a 3,4-dimethylhepta-2,4-dienal side chain, and an acetylated terminal amine. Four total syntheses of **25** have been reported[12] in the literature in recent years.

The synthesis of the tetrahydropyran unit **35** commenced with an asymmetric aldol addition reaction of thiazolidinethione propionate **27**[13] to the benzyloxybutanal **26** using $TiCl_4$ and (−)-sparteine as the base. This led to aldol product **28** in 90% isolated yield. The secondary hydroxyl group of **28** was protected as silyl ether **29** using TBSOTf and 2,6-lutidine. Treatment of thioimide **29** with DIBAL-H[14] followed by Wittig olefination furnished α,β-unsaturated ester **30** in 88% yield over two steps. Hydrogenation of **30** using Pd/C in EtOAc failed to give the saturated ester **31**. It is assumed that the catalyst was poisoned by the presence of the residual thiozolidinethione auxiliary, which had proved to be difficult to fully separate from ester **30** by chromatography (Scheme 3).

Scheme 3. Synthesis of α,β-Unsaturated Ester **30**

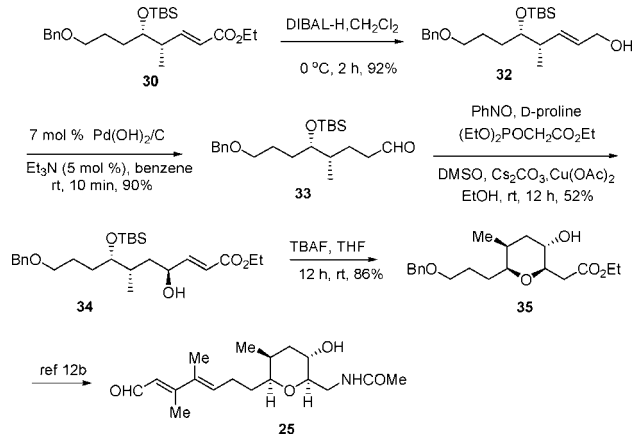


The ester group in compound **30** was therefore reduced using DIBAL-H to provide *E*-allylic alcohol **32** (Scheme 4).

(11) Satake, M.; Bourdelais, A. J.; Van Wagoner, R. M.; Baden, D. G.; Wright, J. L. *Org. Lett.* **2008**, *10*, 3465–3468.

(12) (a) Kuranaga, T.; Shirai, T.; Baden, D. G.; Wright, J. L.; Satake, M.; Tachibana, K. *Org. Lett.* **2009**, *11*, 217–220. (b) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 3950–3952. (c) Ghosh, A. K.; Li, J. *Org. Lett.* **2009**, *11*, 4164–4167. (d) Lee, J.; Panek, J. S. *Org. Lett.* **2009**, *11*, 4390–4393.

Scheme 4. Synthesis of a C5−C13 Tetrahydropyran Ring System **35** of (−)-Brevisamide



The allyl alcohol **32** was subjected to the newly developed methodology to furnish desired saturated aldehyde **33** in one pot in 90% yield along with saturated alcohol in 5% yield. The key tetrahydropyran ring was constructed by means of α-aminoxylation followed by Horner−Wadsworth−Emmons (HWE) reaction of an aldehyde and intramolecular oxa-Michael strategy (IMOM). Thus, direct catalytic asymmetric aminoxylation[15] of the aldehyde **33** by using D-proline as the catalyst and nitrosobenzene as the oxygen source followed by HWE reaction gave aminoxy olefinic ester for which cleavage of the O−N bond was achieved using $Cu(OAc)_2$ in EtOH at room temperature. This resulted in γ-hydroxy-α,β-unsaturated ester **34** in 52% yield (99% *de*). Exposure of the hydroxy enoate **34** to excess TBAF in tetrahydrofuran (THF) at rt for 12 h resulted in deprotection−cyclization in tandem fashion to give the 2,6-*cis* tetrahydropyran **35** as a single isomer in 86% yield. The relative configuration of **35** was assigned by spectral studies and was found identical in all respects to that reported by Lindsley et al.,[12b] which is a known intermediate for the synthesis of the natural product **25**. Since the conversion of tetrahydropyran intermediate **35** into (−)-brevisamide (**25**) is known, this completed its formal total synthesis.

In summary, we have observed the first example of a palladium-catalyzed isomerization of primary allylic alcohols to furnish saturated aldehydes. The approach has been successfully applied for the synthesis of a tetrahydropyran core unit of brevisamide (in seven steps), which completes its formal synthesis. Further applications and extensions of the methodology are currently ongoing in our laboratory and will be reported in due course.

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Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777.

(14) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097–2100.

(15) (a) Sabitha, G.; Chandrashekhar, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3824–3826. (b) Sabitha, G.; Vasudeva Reddy, D.; Senkara Rao, A.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 4195–4198. (c) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697. (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, C. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. (e) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (f) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296. (g) Zhong, G. *Chem. Commun.* **2004**, 606–607. (h) **General procedure for the isomerization of primary allylic alcohols to aldehydes:** A 50 mL two-neck round-bottomed flask was charged with 7 mol % of $Pd(OH)_2/C$. C_6H_6 (3 mL) was added. H_2-gas was passed via a balloon for 30 min (for the activation of the catalyst). The H_2-gas supply was stopped, and stirring continued for 10 min after which a solution of allylic alcohol **1** (0.5 mmol) in C_6H_6 (3 mL) was added. The reaction mixture was stirred for another 10 min. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a Celite pad which was washed with EtOAc (10 mL). The filtrate was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (2−30% EtOAc/hexane as eluent) to afford the aldehyde **2** (88−98% yield).