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New Ring-Expansion Reactions of Hydroxy Propenoyl Cyclic Compounds under Palladium(0)/Phosphine-Catalyzed Conditions

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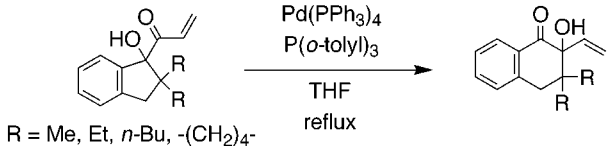
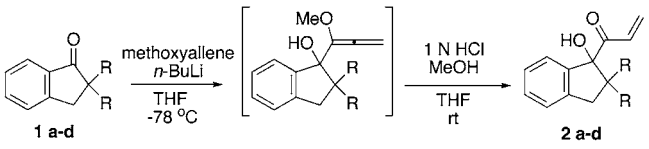
ABSTRACT



Palladium(0)-catalyzed one-atom ring-expansion of 1-hydroxy-2,2-dialkyl-1-propenoylindan derivatives has been achieved in the presence of P(*o*-tolyl)$_3$ giving 2-hydroxy-3,3-dialkyl-2-vinyl-1-tetralone derivatives in excellent yields. This ring-expansion reaction was applied to a 17-(1-oxo-2-propenyl)-*β*-estradiol derivative and furnished a similar ring-expanded product in an excellent yield.

Ring-expansion reactions have provided chemists a considerably useful tool for the construction of various biologically active natural products and drugs.[1] Recent efforts in our laboratory have focused on base-mediated and Pd(0)-catalyzed ring-expansion reactions (5 → 7 and 5 → 6) using various hydroxy allenyl cyclic compounds.[2] Liebeskind and Stone[3a] and the Butenschön group[3b] reported acid (CF_3CO_2H)-catalyzed ring-expansion reactions (4 → 5) of methoxyallenylcyclobutenols via corresponding enone intermediates, thus releasing four-membered ring strain.[3a] However, a similar acid-catalyzed ring-expansion reaction of the 1-hydroxy-2,2-dimethyl-1-propenoylindan **2a** with CF_3CO_2H resulted in a very low yield (6%) of a ring-expanded product **3a** and 89% recovery of **2a**. Conventional reaction conditions using BF_3·OEt_2 and KOH for the well-known α-ketol rearrangement[4] were also not available for the ring-expansion reactions of **2a**. We describe here the first successful demonstration of the Pd(0)- and phosphine-catalyzed one-atom ring-expansion reactions of **2a**−**d** and **9** under neutral conditions.

Scheme 1



a : R = Me, **b** : R = Et, **c** : R = *n*-Bu, **d** : R = -(CH$_2$)$_4$-

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Table 1. One-Atom Ring-Expansion Reactions of 1-Hydroxy-2,2-dialkyl-1-propenoylindans **2a**−**d**

entry	2	Pd (mol %)	additive (mol %)	time (h)	product	yield (%)[a]
1	**2a**	$Pd(PPh_3)_4$ (5.0)		7	**3a**	52[b] (40[b])[c]
2	**2b**	$Pd(PPh_3)_4$ (5.0)		15	**3b**	68[b] (22[b])[c]
3	**2a**	$Pd(PPh_3)_4$ (5.0)	P(*o*-tolyl)$_3$ (10.0)	7	**3a**	92
4	**2b**	$Pd(PPh_3)_4$ (5.0)	P(*o*-tolyl)$_3$ (10.0)	15	**3b**	99
5	**2c**	$Pd(PPh_3)_4$ (5.0)	P(*o*-tolyl)$_3$ (10.0)	18	**3c**	90
6	**2d**	$Pd(PPh_3)_4$ (5.0)	P(*o*-tolyl)$_3$ (10.0)	22	**3d**	80
7	**2a**		P(*o*-tolyl)$_3$ (10.0)	7	**3a**	43[b] (29[b])[c]
8	**2a**		P(*o*-tolyl)$_3$ (30.0)	24	**3a**	71
9	**2a**		PPh_3 (10.0)	7	**3a**	55
10	**2a**		P(*n*-Bu)$_3$ (10.0)	7	**3a**	12
11	**2a**		DPPE (10.0)	7	**3a**	13
12	**2a**		DABCO (10.0)	7	**3a**	23[b] (trace[b])[c]
13	**2a**		DBU (10.0)	7	**3a**	53
14	**2a**		Et_3N (10.0)	7	**3a**	25[b] (45[b])[c]
15	**2a**		Me_2S (10.0)	7	**3a**	13[b] (71[b])[c]
16	**2b**		P(*o*-tolyl)$_3$ (10.0)	15	**3b**	62[b] (27[b])[c]
17	**2a**	$PdCl_2(MeCN)_2$ (5.0)		24	**3a**	26[b] (44[b])[c]
18	**2a**	$PdCl_2(MeCN)_2$ (5.0)	P(*o*-tolyl)$_3$ (10.0)	24	**3a**	28[b] (13[b])[c]
19	**2a**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)		24	**3a**	5[b] (67[b])[c]
20	**2a**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	P(*o*-tolyl)$_3$ (10.0)	7	**3a**	83

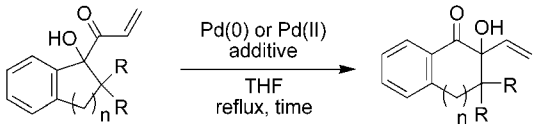
[a] Isolation yield. [b] ^{1}H NMR (400 MHz, $CDCl_3$) analysis. [c] Recovery of starting material.

The precursor compounds **2a**−**d** were prepared in 75−88% yields by treatment of the corresponding dialkylindanones **1a**−**d**[5] with lithio methoxyallene, followed by hydrolysis with 1 N HCl in MeOH−THF (Scheme 1).[6,7]

First, **2a** was refluxed for 7 h in the presence of 5 mol % $Pd(PPh_3)_4$ alone in THF. The desired one-atom ring-expansion reaction proceeded to afford the 2-hydroxy-3,3-dialkyl-2-vinyl-1-tetralone derivative **3a** in 52% yield, but **2a** (40%) was recovered (entry 1 in Table 1). Similar treatment of **2b** for 15 h gave **3b** in 68% yield, together with 22% recovery of **2b** (entry 2 in Table 1). These results suggested the decomposition of the Pd catalyst under the reaction conditions used. Thus, **2a** was refluxed for 7 h in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % P(*o*-tolyl)$_3$ as an additive,[8] which is known to stabilize Pd catalysts and improve turnover in THF. The desired ring-expansion reaction proceeded smoothly to afford **3a** in 92% yield (entry 3 in Table 1). Then, similar reactions of **2b**−**d** using 5 mol % $Pd(PPh_3)_4$ and 10 mol % P(*o*-tolyl)$_3$ furnished **3b** in 99% yield, **3c** in 90% yield, and **3d** in 80% yield, respectively (entries 4−6 in Table 1). All experimental results are summarized in Scheme 2 and Table 1.

The structures of all ring-expanded products **3a**−**d** were explicitly determined by their characteristic spectroscopic data and/or by X-ray crystallographic analysis of **3a**, as shown in Figure 1.[7,9] Treatment of the six- and seven-membered compounds **4a** and **5a**, respectively, with 5 mol % $Pd(PPh_3)_4$ and 10 mol % P(*o*-tolyl)$_3$ in THF under reflux for 24 h led only to recovery of each corresponding starting compound in either 79 or 90% yield.

Scheme 2



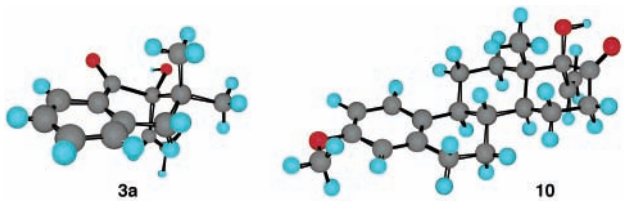


Figure 1. Computer-generated drawing from the X-ray coordinates of compounds **3a** and **10**.

To clarify the ring-expansion mechanism, several reactions were carried out as follows. Compounds **2a**,**b** were allowed

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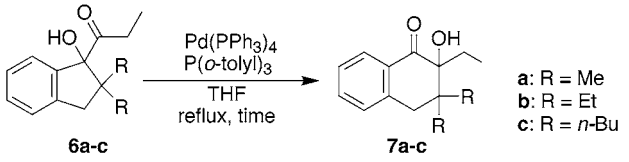
(7) See also Supporting Information.
(8) For review, see: Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

(9) X-ray data for **3a**: $C_{14}H_{16}O_2$, MW = 216.28, colorless needle, monoclinic, space group $P2_1/c$ (#14), a = 13.2235(4) Å, b = 10.1349(5) Å, c = 18.0755(5) Å, V = 2298.0(2) Å^3, β = 108.443(4)°, Z = 8, R = 0.131, Rw = 0.061. Structure factors are available from author upon request.

to react with several Lewis bases [e.g., P(*o*-tolyl)$_3$, PPh$_3$, 1,2-bis(diphenylphosphino)ethane (DPPE), DABCO, DBU, Et$_3$N, Me$_2$S], which are commonly employed in the traditional Morita−Baylis−Hillman reaction,[10] in THF under reflux without the use of Pd(PPh$_3$)$_4$ to give **3a** or **3b** in 12−71% yields, respectively (entries 7−16 in Table 1). On the basis of recent reports[11] that the propenoyl moiety can coordinate to Pd(II), **2a** was treated with PdCl$_2$(MeCN)$_2$ alone or a mixture of PdCl$_2$(MeCN)$_2$ and P(*o*-tolyl)$_3$. These reactions gave **3a** in 26 and 28% yields, respectively, together with the recovery of **2a** (entries 17 and 18 in Table 1). Upon treatment with Pd$_2$(dba)$_3$·CHCl$_3$ alone as a Pd(0) catalyst, the reaction of **2a** scarcely proceeded (entry 19 in Table 1), but in the presence of P(*o*-tolyl)$_3$, the yield of **3a** was improved to 83% (entry 20 in Table 1). Thus, it was demonstrated that the Pd(0) species were essential catalysts, and the Pd(0)-catalyzed ring-expansion reaction required an efficient additive such as P(*o*-tolyl)$_3$. Subsequently, we investigated the importance of the C=C bond in the propenoyl moiety of **2a**−**c**. 1-Hydroxy-1-propanoylindan derivatives **6a**−**c**, obtained by the catalytic hydrogenation of **2a**−**c**, were subjected to the same reaction conditions as described above, but the corresponding α-tetralone derivatives **7a**−**c** were obtained in scant amounts, as shown in Table 2. When **6a** was refluxed in the presence of 50 mol

Table 2. Attempt at Ring-Expansion Reactions of 1-Hydroxy-1-propanoylindans **6a**−**c**



6a-c 7a-c

entry	6	Pd(PPh$_3$)$_4$ (mol %)	P(*o*-tolyl)$_3$ (mol %)	time (h)	product	yield (%)[a]
1	**6a**	5	10	7	**7a**	10 (87)[b]
2	**6a**	50	100	24	**7a**	88[c]
3	**6b**	5	10	15	**7b**	12 (78)[b]
4	**6c**	5	10	18	**7c**	8 (92)[b]

[a] ^{1}H NMR (400 MHz, CDCl$_3$) analysis. [b] Recovery of starting material. [c] Isolation yield.

% Pd(PPh$_3$)$_4$ and 100 mol % P(o-tolyl)$_3$ in THF, **7a** could be obtained in 88% yield. These results suggested that the presence of the C=C bond in the conjugated propenoyl moiety of **2a**−**c** was very efficient in the Pd(0)- and P(*o*-tolyl)$_3$-catalyzed ring-expansion reactions.

Speculative mechanisms for the Pd(0)- and phosphine-catalyzed ring-expansion reactions can be suggested on the basis of the experimental results described above (Figure 2).[2f,10−13] In the first step of the catalytic cycle, the oxidative

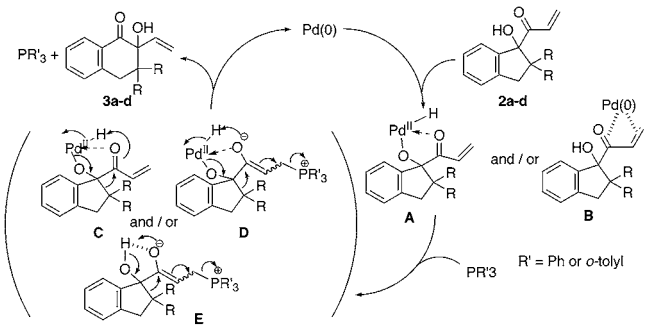


Figure 2. Plausible mechanisms for the Pd(0)- and phosphine-catalyzed ring-expansion reactions of **2a**−**d**.

addition of the hydroxy group of **2a**−**d** to a Pd(0) catalyst generates the complex **A**,[2f,11−13] in which the reductive elimination of the Pd(II) species, followed by migration of the C1−C2 bond in a concerted manner (**C**), may give the ring-expanded products **3a**−**d**.

Conjugate addition of the phosphine species to the propenoyl moiety of **A** may form complex **D**,[10] in which synchronous release of the Pd(II) species and the phosphonium moiety, followed by the migration of the C1−C2 bond, would afford **3a**−**d**. In another plausible first step of the catalytic cycle, the coordination of the propenoyl moiety of **2a**−**d** to the Pd(0) species may generate the weak complex **B**, whereby the easy conjugate addition of the phosphine species[10] may generate the phosphonium intermediate **E**. In **E**, hydrogen abstraction from the C1−OH group by the resulting enolate, followed by ketonization and release of the phosphonium moiety, would occur, together with synchronous double-bond migration and C1−C2 bond migration to give **3a**−**d**.

The *β*-ketol rearrangement reaction of 17-hydroxy-20-ketosteroids, referred to as the *D*-homo rearrangement, was discovered in 1938 and has been the subject of investigation ever since its discovery.[14] Although all rearrangement reactions of steroidal compounds are typically performed by employing various bases and Lewis acids,[14] such a neutral Pd(0)- and phosphine-catalyzed rearrangement reaction has never been reported. Hence, we attempted the ring-expansion reaction of 17-(1-oxo-2-propenyl)-*β*-estradiol derivative **9**

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(11) (a) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S. I. *Chem. Lett.* **1989**, 2001. (b) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960. (c) Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403.

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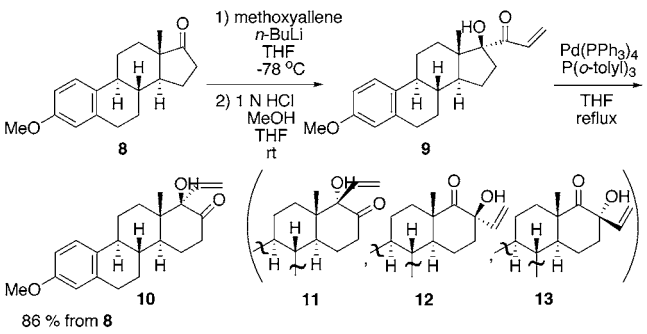
(13) (a) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365. (b) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270. (c) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207.

(14) (a) Ruzicka, L.; Meldahl, H. F. *Helv. Chim. Acta* **1938**, *21*, 1760. (b) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932. (c). Bischofberger, N.; Walker, K. A. M. *J. Org. Chem.* **1985**, *50*, 3604. (d) Schor, L.; Seldes, A. M. S.; Gros, E. G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 163. (e) Paryzek, Z.; Martynow, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 823.

(vide infra), which was prepared from **8**, as shown in Scheme 3. Crude compound **9**, without being purified on a silica gel

Scheme 3



column, was refluxed in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % P(*o*-tolyl)$_3$ in THF for 24 h. The desired ring-expansion reaction proceeded in a stereospecific manner to afford the sole product **10** in 86% yield from **8** among four possible products, **10**−**13** (Scheme 3). The structure of **10** was clarified by X-ray crystallographic analysis, as shown in Figure 1.[7,15]

On the basis of the stereochemistry (^{1}H NOESY experiment shown in Figure 3) of the precursor **9** and the product

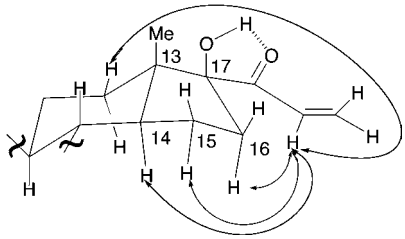


Figure 3. Selected ^{1}H NMR NOE enhancement for **9**.

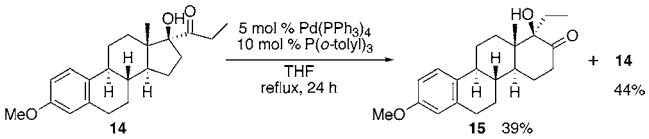
10, it becomes evident that the ring-expansion reaction proceeded by the stereospecific migration of the C13−C17 bond rather than by that of the C16−C17 bond.

(15) X-ray data for **10**: $C_{22}H_{28}O_3$, MW = 340.46, colorless plate, orthorhombic, space group $P2_12_12_1$ (#19), a = 7.4067(3) Å, b = 7.8333(2) Å, c = 30.5900(9) Å, V = 1774.80(10) Å^3, Z = 4, R = 0.065, Rw = 0.115. Structure factors are available from author upon request.

To confirm the importance of the conjugated propenoyl system in the Pd(0)- and phosphine-catalyzed ring-expansion of **9**, compound **14**, which was obtained by hydrogenation of **9**, was refluxed for 24 h under the same conditions as those used in the case of **9**. The ring-expansion reaction proceeded to afford **15** in 39% yield, but 44% of **14** was recovered (Scheme 4). This result suggested that the C=C bond of the conjugated propenoyl moiety played an important role; thus, the Morita−Baylis−Hillman reaction[10] appeared to be involved in the Pd(0)- and phosphine-catalyzed ring-expansion reaction. The structure and stereochemistry of **15** were determined by its identification with the product, which was prepared by catalytic hydrogenation of **10**.[7] Thus, the Pd(0)- and phosphine-catalyzed ring-expansion reaction of **9** can be similarly explained in terms of the case of **2a**−**d**, as shown in Figure 2.

In conclusion, we demonstrated new Pd(0)- and P(*o*-tolyl)$_3$-catalyzed one-atom ring-expansion reactions of 1-hydroxy-2,2-dialkyl-1-propenoylindan derivatives and a steroidal compound. These new reactions are expected to be useful for the construction of cyclohexanones bearing vinyl and hydroxy groups and for further allylic rearrangement.[16]

Scheme 4



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Supporting Information Available: Typical experimental procedure for the synthesis of compounds **1b**,**c**, **2a**−**d**, **3a**, **4a**, **5a**, **6a**−**c**, **7a**, **9**, **10**, **14**, and **15** and their physical and spectroscopic data, as well as X-ray structural data of compounds **3a** and **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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