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Palladium-catalyzed 1,3-diol fragmentation: synthesis of ω-dienyl aldehydes†‡

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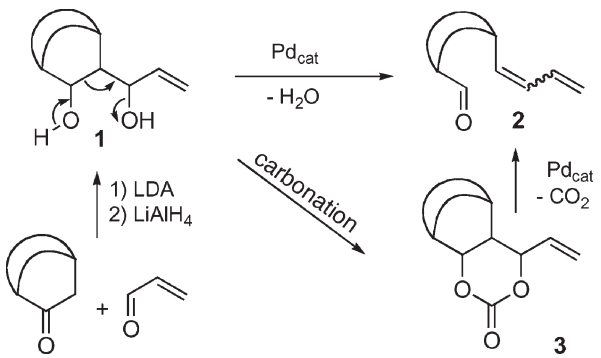
2-(1′-Hydroxy-2′-propenyl)cycloalkan-1-ols 1 undergo dehydrative C1–C2 bond cleavage and provide ω-dienyl aldehydes 2 under the catalysis of Pd(0) and 9-phenyl-9-BBN.

ω-Dienyl aldehydes **2** have been utilized as the key strategic intermediates for the synthesis of natural[1] and non-natural products.[2] Accordingly, development of efficient preparation methods of **2** is highly desirable. Just 10 years ago, we reported that under the catalysis of palladium(0) a variety of cyclic carbonates **3** could be smoothly transformed into **2** in good yields *via decarboxylative* fragmentation, triggered by oxidative addition of Pd(0) to the allylic C–O bond (Scheme 1).[3] Very recently nickel(0) catalysts have been proven to work similarly well or much better, providing **2** in excellent yields and with higher *E*-selectivity regarding the diene moiety.[4]

Here, we would like to disclose a new and efficient short cut to the ω-dienyl aldehydes **2** from diols **1** based on palladium-catalyzed *dehydration* fragmentation (Scheme 1). This diol variant (**1** → **2**) is apparently superior over the cyclic carbonate method (**1** → **3** → **2**), not only simply because we can save one step (carbonation), but also because we can utilize even the stereoisomers of diols **1** that are unable to form **3** owing to steric reasons. The diols **1** of a wide structural variety are available straightforwardly in excellent yields *via* a two step sequence from commercially available mono- and bicyclic ketones and α,β-unsaturated aldehydes (Scheme 1).

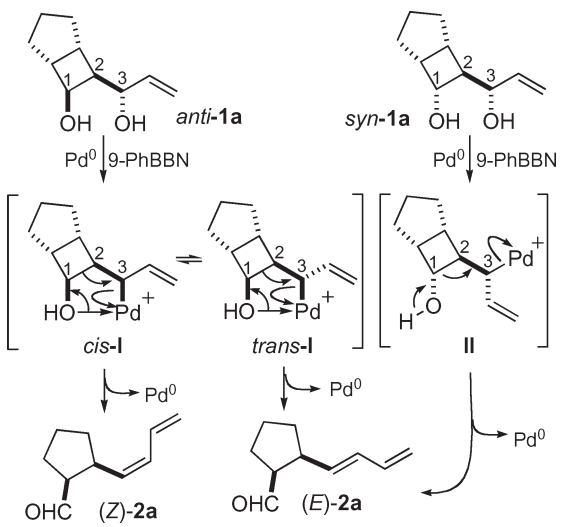


Scheme 1 Pd-catalyzed formation of ω-dienyl aldehydes **2** *via* dehydration of **1** or decarboxylation of **3**.

The idea for this diol variant stems from our previous findings[5] that an allylic alcohol can be catalytically transformed into a π-allylpalladium species in the presence of triethylborane (Et_3B, Scheme 2). The palladium(II) of the thus formed π-allylpalladium intermediate **I** or **II** might serve as a leaving group to facilitate the Grob-type fragmentation[6] as indicated by mechanistic arrows, thereby regenerating a catalytically active Pd(0) species (*vide infra*).

Unexpectedly, however, treatment of a diol **1n** with Et_3B under standard conditions (footnote *a*, Table 1)[5] that have been successfully applied to generate a π-allylpalladium species from an allylic alcohol only caused hydrolysis of Et_3B and provided ethylboronic acid ester **4a** (entry 1, Table 1).[7] The hydrolysis took place instantaneously at ambient temperature. Unlike the corresponding cyclic carbonic acid ester **3**,[3,4] the boronic acid ester **4a** was very reluctant to undergo fragmentation and remained unchanged despite long heating at 110 °C. In order to facilitate oxidative addition of Pd(0) to the allylic C–OH bond of **1n**, Ph_3B, which has higher Lewis acidity, was examined. However, it showed only marginal success and provided an expected fragmentation product **2n**, albeit in a poor yield, along with a phenylboronic acid ester **4b** as the major product (entries 2 and 3). Surprisingly, however, with $(C_6F_5)_3B$ no reaction took place at all and **1n** was recovered quantitatively (entry 4).[8]

Next, we examined 9-phenyl-9-borabicyclo[3.3.1]nonane (9-PhBBN) in expectation that its bicyclic structure should inhibit **1n** from chelation coordination to the boron and hence could



Scheme 2 The most plausible reaction mechanism.

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† This paper is dedicated to the late Professor Yoshihiko Ito for his great contribution to the development of synthetic methodology.

‡ Electronic supplementary information (ESI) available: General procedure and spectral data including ^{1}H NMR spectra for all new compounds. See DOI: 10.1039/b708526e

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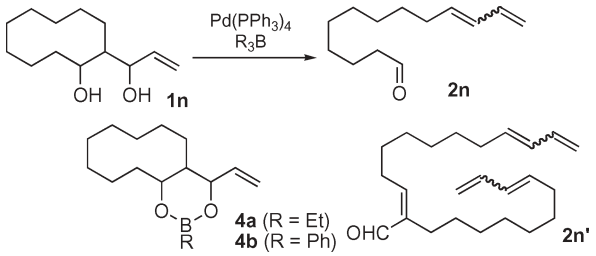
Table 1 Effects of organoboranes on the palladium-catalyzed Grob-type fragmentation of **1n**[a]



Entry	Borane (equiv.)	Solvent[b]	Temp. /°C (*t*/h)	% Yield of **2**/**2′**/**4**
1	Et_3B (3.6)	Tol	110 (24)	**4a**: 64
2	Ph_3B (3.6)	Tol	110 (24)	**2n**:[c] 12, **4b**: 64
3	Ph_3B (3.6)	THF	55 (24)	**2n**:[c] 12, **4b**: 71
4	$(C_6F_5)_3B$ (1.2)	THF	55 (60)	NR[d]
5	9-PhBBN (1.2)	Tol	50 (12)	**2n**:[c] 15, **2n′**: 54
6	9-PhBBN (0.5)	Tol	50 (45)	**2n**:[c] 23, **2n′**: 64

[a] Reaction conditions: **1n** (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), and an organoborane (indicated amount, 9-PhBBN = 9-phenyl-9-borabicyclo[3.3.1]nonane) in a solvent (2.5 mL) at the temperature and for the period of time indicated under N_2. [b] Tol stands for toluene. [c] *E* : *Z* = *ca.* 3–4 : 1. [d] No reaction.

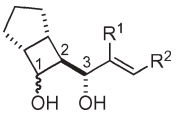
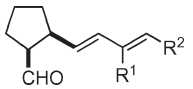
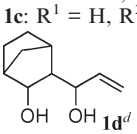
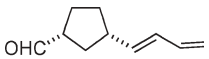
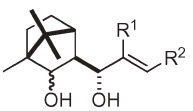
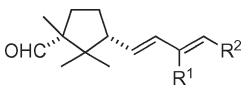
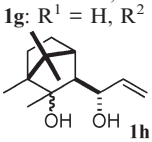
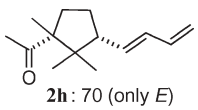
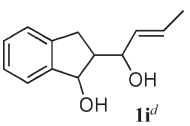
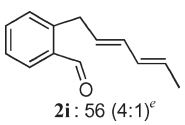
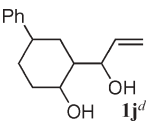
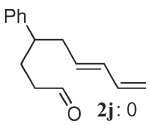
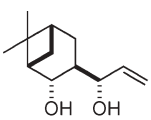
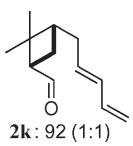
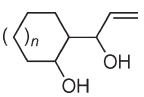
retard hydrolysis. Indeed, no hydrolysis was observed at all, and the expected ω-dienyl aldehyde **2n** was produced as a mixture with its aldol condensation product **2n′** in a 69% combined isolated yield (entry 5). A sub-stoichiometric amount of 9-PhBBN showed apparently better results and provided a mixture of **2n** and **2n′** in an 87% combined isolated yield (entry 6).[9,10]

With the protocols in hand, a variety of diols **1a**–**m**, mixtures of diastereomers, with the exception of *syn*-**1k**, were examined under the conditions of entry 6, Table 1. The results are summarized in Table 2.§ These diols were used after purification by means of column chromatography over silica gel of the reaction mixtures prepared according to Scheme 1.[11]

It should be noted that, on carbonation of a 1 : 1 mixture of *syn*-**1a** and *anti*-**1a**, only *anti*-**1a** provided the corresponding cyclic carbonate *anti*-**3a** in a quantitative yield. *syn*-**1a** failed to provide *syn*-**3a** probably owing to the steric constraint associated with a *trans*-fused bicyclo[4.2.0]octane skeleton in the product (Fig. 1). In this context, the high yield for formation of **2a** from a mixture of *syn*-**1a** and *anti*-**1a** (entry 1, Table 2) clearly indicates the superiority of the present dehydration fragmentation method over the decarboxylation method.[3,4] A similar discussion may hold for other bicyclic diols in Table 2. Particularly, the example shown in entry 11, Table 2 may highlight the utility of the present dehydration method; a diol *syn*-**1k** was produced exclusively as a single diastereomer in an 85–95% overall yield through the cross-aldol reaction of the lithium enolate of nopinone with acrolein and then $LiAlH_4$ reduction. Like the case of *syn*-**1a**, the cyclic carbonate of *syn*-**1k** was not obtained at all probably owing to steric reasons; one of the two methyl groups of *syn*-**1k** might be forced to experience severe steric repulsion against the C2–H hydrogen on carbonation (Fig. 1). Yet, under the standard dehydration conditions, the diol *syn*-**1k** smoothly underwent fragmentation to yield **2k** in a remarkably good yield (entry 11).

Table 2 summarizes the results in order of the increasing ring size of the cycloalkanols, ranging from 4- to 8-membered rings (for a 10-membered ring, see Table 1). Like **1n**, 1,3-diols **1l** and **1m**,

Table 2 Pd(0)-catalyzed dehydration fragmentation of diols **1**[a]

Entry	Diol **1** (isomer ratio)[b]	*t*/h	ω-Dienyl aldehyde **2** isolated yield (%) (*E* : *Z*)[c]
			
1	**1a**: R^1 = H, R^2 = H (1 : 1)	12	**2a**: 87 (11 : 1)
2	**1b**: R^1 = Me, R^2 = H (1 : 1)	24	**2b**: 68 (only *E*)
3	**1c**: R^1 = H, R^2 = Me[d]	24	**2c**: 80 (2 : 1)[e]
4	 **1d**[d]	24	 **2d**: 81 (4:1)
			
5	**1e**: R^1 = H, R^2 = H (1 : 3)	2	**2e**: 94 (only *E*)
6	**1f**: R^1= Me, R^2 = H (1 : 4)	48	**2f**: 78 (only *E*)
7	**1g**: R^1 = H, R^2 = Ph (1 : 1.6)	48	**2g**: 81 (8 : 1)[f]
8	 **1h** (1:7)	24	 **2h**: 70 (only *E*)
9	 **1i**[d]	30	 **2i**: 56 (4:1)[e]
10	 **1j**[d]	36	 **2j**: 0
11	 **1k** (only *syn*)	24	 **2k**: 92 (1:1)
			See Table 1 for the structures of products
12	**1l** (*n* = 2)[d]	48	**2l**: 1 (7 : 1), **2l′**: 59
13	**1m** (*n* = 3)[d]	24	**2m**: 15 (5 : 1), **2m′**: 54

[a] Reaction conditions: a diol **1** (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), and 9-PhBBN (50 mol%) in toluene (2.5 mL) at 50 °C for the period of time indicated under N_2. [b] *syn* : *anti* ratio regarding C1 and C3 hydroxy groups. [c] The isomer ratios of **2** were determined on the basis of ^1H NMR (400 MHz) after purification by means of column chromatography over silica gel. [d] A complex mixture of isomers. [e] *EE* : *EZ* ratio. [f] *EE* : *ZE* ratio.

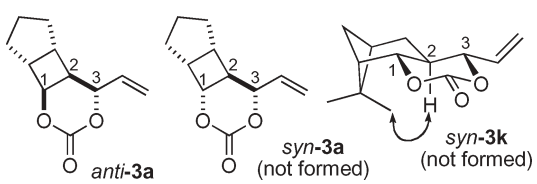


Fig. 1 Cyclic carbonates.

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giving rise to ω-dienyl aldehydes bearing no α-substituents, provided aldol condensation products **2l′** and **2m′**,[9] respectively, as the major products. Cyclohexanol derivative **1j** was exceptionally robust and was recovered unchanged even after long heating at 50 °C (entry 10).[9] Cyclopentanol derivative **1i** showed a somewhat low yield (entry 9). In sharp contrast to these, bicyclic diols **1d**–**h** and **1k** containing cyclohexanol and/or cyclopentanol structural motifs smoothly underwent fragmentation and provided the expected ω-dienyl aldehydes **2** in good to excellent yields (entries 4–8 and 11). Cyclobutanol derivatives **1a**–**c** reacted similarly well. These results suggest that ring strain or torsional strain in the cycloalkanols is a key factor to promote the dehydration fragmentation successfully. It should be also noted that the present method is applicable to the synthesis of ω-dienyl ketones **2h** (entry 8).

The most plausible mechanism is outlined in Scheme 2 using **1a** as a representative of the diols. Oxidative addition of Pd(0) to the allylic C–OH bond of *anti*-**1a**, activated by the coordination of 9-PhBBN, with inversion of configuration would provide a *cis*-oxapalladacyclopentane intermediate *cis*-**I**, being *cis* with respect to the C2- and C3-substituents, as a primary intermediate, which would lead to (*Z*)-**2a** on fragmentation. However, the selective formation of (*E*)-**2a** over (*Z*)-**2a** (entry 1, Table 2) suggests that *cis*-**I** would rather isomerize to a sterically less congested, more stable *trans*-**I** *via* a σ–π–σ isomerization mechanism than undergo fragmentation into (*Z*)-**2a**. Fragmentation through *trans*-**I** leads to (*E*)-**2a**. For the fragmentation of *syn*-**1a**, it is sterically impossible for the allylpalladium intermediate to form a cyclic structure like **I** owing to the severe strain imposed on a *trans*-fused bicyclo[3.2.0]heptane skeleton, and hence it might undergo fragmentation through an open-chain intermediate **II**, with an *anti* conformation regarding C1–C2 and C3–Pd bonds, and furnish (*E*)-**2a** selectively.

The difference in reaction features between the decarboxylation and dehydration methods, *e.g.*, **3j** → **2j** (42%)[3,9] under Pd(0) catalysis and **3j** → **2j** (84%)[4,9] under Ni(0) catalysis, while **1j** → **2j** (0%, entry 10, Table 2), may be primarily attributed to the structural differences in the intermediates **I**. An anionic charge developed on the oxygen in **I** (O^- instead of OH) during decarboxylation might weaken the C1–C2 bond[12] and hence facilitate the fragmentation. On the other hand, the oxygen in **I** generated through dehydration may be mostly neutral, and hence considerable amount of ring strain may be required to weaken the C1–C2 bond.

The Grob-type fragmentation of 1,3-diols (*e.g.*, **1** → **2**) is among the very powerful tools available for the construction of desired molecules.[6] However, harsh reaction conditions, either strongly basic or acidic and/or high reaction temperatures, have limited its wide use.[13] Transition metal catalysis has been so far only effective for the ring opening reaction of some strained cyclopropanol and cyclobutanol derivatives.[14] In this context, it should be noted that the present palladium-catalyzed reaction is the first example, to the best of our knowledge, that demonstrates the ring-opening of an array of cycloalkanols, ranging from cyclobutanol to cyclodecanol with the exception of cyclohexanol, under essentially neutral conditions.[16]

Notes and references

§ General procedure (see ESI for details‡): into a flask containing $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) purged with N_2 were added dry toluene (2.5 mL), *syn*-**1k** (98.1 mg, 0.5 mmol), and 9-PhBBN (0.8 mL, 0.3 M solution, 0.25 mmol)[15] *via* syringe at rt. The solution was stirred at 50 °C for 24 h under N_2. After usual work-up and purification, **2k** was isolated in 92% yield (80.2 mg).

1 (*a*) Y. Sato, N. Saito and M. Mori, *Tetrahedron*, 1998, **54**, 1153; (*b*) N. Waizumi, T. Itoh and T. Fukuyama, *Tetrahedron Lett.*, 1998, **39**, 6015; (*c*) Y. Sato, M. Takimoto and M. Mori, *Synlett*, 1997, 734.

2 (*a*) C.-M. Yu, J. Youn, S.-K. Yoon and Y.-T. Hong, *Org. Lett.*, 2005, **7**, 4507; (*b*) Y. Sato, N. Saito and M. Mori, *J. Org. Chem.*, 2002, **67**, 9310; (*c*) K. Shibata, M. Kimura, M. Shimizu and Y. Tamaru, *Org. Lett.*, 2001, **3**, 2181.

3 H. Harayama, T. Kuroki, M. Kimura, S. Tanaka and Y. Tamaru, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2352.

4 M. Mori, M. Kimura, Y. Takahashi and Y. Tamaru, *Chem. Commun.*, 2006, 4303.

5 (*a*) M. Kimura, M. Fukasaka and Y. Tamaru, *Heterocycles*, 2006, **67**, 535; (*b*) M. Kimura, M. Futamata, R. Mukai and Y. Tamaru, *J. Am. Chem. Soc.*, 2005, **127**, 4592. For a review, see: (*c*) Y. Tamaru, *Eur. J. Org. Chem.*, 2005, 2647.

6 Review on the Grob fragmentation: T. Constantieux and J. Rodriguez, *Sci. Synth.*, 2004, **26**, 413.

7 Et_3B is usually stable toward hydrolysis with alcohols. Hence, the hydrolysis of Et_3B with **1n** might be attributed to chelation coordination of **1n** (and **1e**, see ref. 8) to boron. However, the hydrolysis by a 1,3-diol seems to be the subject of some subtle stereoelectronic effects of diols, since Et_3B withstands hydrolysis with some 1,3-diols, see: R. Mukai, Y. Horino, S. Tanaka, Y. Tamaru and M. Kimura, *J. Am. Chem. Soc.*, 2004, **126**, 11138.

8 The reaction features described here seem to be general for other diols. For example, similar results were obtained for the reactions of **1e** with Et_3B, Ph_3B, and $(C_6F_5)_3B$.

9 Isolated yields observed for the Pd-catalyzed decarboxylation:[3] **2j** (42%), **2m** (54%), **2n** (85%). Isolated yields observed for the Ni-catalyzed decarboxylation:[4] **2j** (84%), **2m** (94%), **2n** (85%).

10 Use of both $Pd(PPh_3)_4$ and 9-PhBBN is essential to promote the dehydrative fragmentation. In the absence of either of them, neither **2n** nor **2n′** was formed at all.

11 X-Ray crystallographic data of *anti*-**1e** and *syn*-**1k** (relative stereochemistry) were obtained. CCDC 639709 and 631058, respectively. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b708526e.

12 Review on oxy-Cope rearrangement: T. Constantieux and J. Rodriguez, *Sci. Synth.*, 2004, **26**, 413.

13 For the $BF_3{\cdot}OEt_2$ catalyzed synthesis of ω-dienyl aldehydes from acetonides of 1,3-*anti*-diols of close structural similarity to **1k**, see: J. Barluenga, M. Álvarez-Pérez, K. Wuerth, F. Rodriguez and F. J. Fañanás, *Org. Lett.*, 2003, **5**, 905.

14 (*a*) M. Murakami, S. Ashida and T. Matsuda, *J. Am. Chem. Soc.*, 2006, **128**, 2166. For a review on palladium-catalyzed C–C bond cleavage reaction, see: (*b*) T. Nishimura and S. Uemura, *Synlett*, 2004, 201.

15 G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, 1974, **73**, 1.

16 We thank financial support from the Ministry of Education, Culture, Sports, Science and Technology, Japanese Government [Grant-in-Aid for Scientific Research (B) 19350050 and Priority Areas 17035065 and 18037059].

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