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An unexpected palladium-catalyzed cyclization of bis-hydroxy allylic alcohols to dioxabicyclo[2.2.2]octanes

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Abstract—The palladium(II)-catalyzed cyclization of bis-hydroxy allylic alcohols afforded quantitatively a mixture of (3-alkyl-5-vinyltetrahydrofuran-3-yl)methanol and 4-alkyl-1-methyl-2,6-dioxabicyclo[2.2.2]octane.

Transition-metal-catalyzed heterocyclization reactions of unsaturated substrates is now a well used methodology in organic synthesis, allowing highly valuable oxygen- and nitrogen-heterocyclic derivatives.[1,2] Particularly, intramolecular nucleophilic attack of oxygen nucleophiles to palladium π-olefin complexes[3,4] or palladium η^3-allyl complexes[5] afforded the corresponding oxygen heterocycles generally in a stereo- and regioselective manner.

Recently, Uenishi et al.[6] reported the synthesis of tetrahydro- and 3,6-dihydro[2*H*]pyrans via the palladium(II)-catalyzed cyclization of monohydroxy allylic alcohols. In order to obtain functionalized tetrahydrofuran derivatives, we planned to apply this methodology to bis-hydroxy allylic alcohols as starting materials. We described herein preliminary results obtained in this palladium(II)-catalyzed cyclization.

Initial experiments were performed using bis-hydroxy allylic alcohol **1a** (as a 80/20 mixture of *E*/*Z* isomers) as a model substrate. This substrate was prepared by palladium-catalyzed alkylation of dimethyl benzylmalonate with the monoacetate of buten-1,4-diol, followed by protection of the hydroxyl function via a *tert*-butyldimethylsilyl group, then reduction of the diester, and finally deprotection of the *tert*-butyldimethyl ether. The cyclization was attempted in the presence of 5 mol % of $PdCl_2(CH_3CN)_2$ in THF at rt and was found to afford the expected stereoisomeric tetrahydrofurans **2a** and **3a**, and more surprisingly dioxabicyclo[2.2.2]octane **4a**, as a 32/68 mixture (Scheme 1, Table 1, entry 1). The relative stereochemistry of epimers **2a** and **3a** was identified by ^{1}H NMR;[7] a NOESY sequence on the major isomer **2a** indicates clearly that the proton H-5 at δ 4.41 ppm and the protons of the CH_2OH group at δ 3.48 ppm are close to each other, which is not the case for the benzylic protons at δ 2.78 and 2.88 ppm, showing unambiguously that this isomer was the *rac*-(3*S**,5*S**)-compound.

The solvent seems crucial for the formation of the dioxabicyclo[2.2.2]octane **4a** as the main compound, since the use of CH_3OH, CH_2Cl_2, CH_3CN, or C_6H_6 gave predominantly the tetrahydrofuran derivatives **2a** and **3a**, as a 1:1 mixture of the two stereoisomers (Table 1, entries 2–5).

In order to extend the scope of this methodology, allowing an easy access to dioxabicyclo[2.2.2]octanes, we prepared various bis-hydroxy allylic alcohols **1b–h** bearing different substituents and studied their cyclization in THF in the presence of 5% of $PdCl_2(CH_3CN)_2$. Bishydroxy allylic alcohol **1b**, bearing a 2-naphthylmethyl group, afforded the corresponding dioxabicyclo[2.2.2]-octane **4b** in 78% chemical yield, together with only 19% of tetrahydrofuran **2b** (Table 1, entry 6). Since compound **4b** gave very nice crystals, we could confirm unambiguously its structure by X-ray crystallographic analysis (Fig. 1).[8] Bishydroxy allylic alcohols **1c** (R = 4-$CH_3C_6H_4$), **1d** (R = 2-$CH_3C_6H_4$), and **1f**

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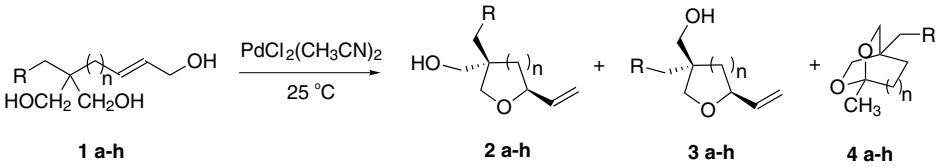


a: n = 1, R = C_6H_5
b: n = 1, R = 2-naphtyl
c: n = 1, R = 4-CH_3-C_6H_4
d: n = 1, R = 2-CH_3-C_6H_4
e: n = 1, R = C_6H_5-CH=CH-
f: n = 1, R = C_6H_{11}
g: n = 1, R = CH_3
h: n = 2, R = C_6H_5

Scheme 1.

Table 1. Cyclization of bis-hydroxy allylic alcohols **1** using $PdCl_2(CH_3CN)_2$ as the catalyst

Entry	Compound **1**	Solvent	Yield **2**+**3** (%)[a]	**2** (%)/**3** (%)[b]	Yield **4** (%)[a]
1	**1a**	THF	32	90/10	68
2	**1a**	CH_3OH	63	53/47	30
3	**1a**	CH_2Cl_2	83	48/52	14
4	**1a**	CH_3CN	86	46/54	13
5	**1a**	C_6H_6	80	48/52	15
6	**1b**	THF	19	100/0	78
7	**1c**	THF	31	91/9	61
8	**1d**	THF	23	91/9	75
9	**1e**	THF	75	80/20	19
10	**1f**	THF	36	93/7	60
11	**1g**	THF	51	73/27	46
12	**1h**	THF	72	43/57	23

[a] Chemical yield after column chromatography.
[b] Determined by ^1H NMR.

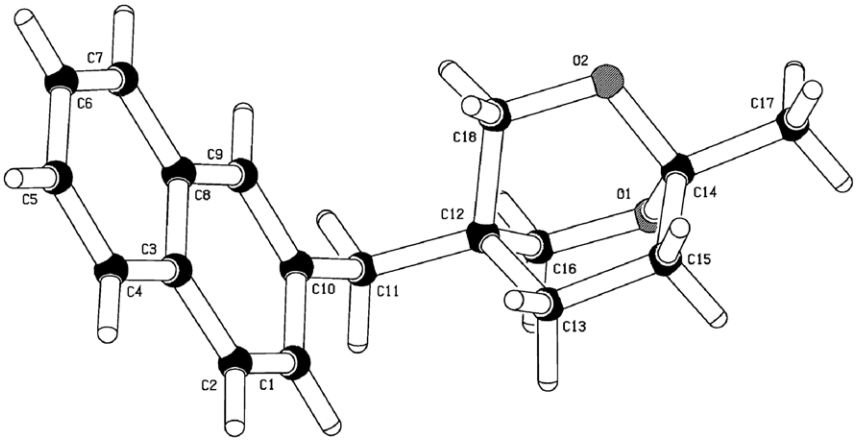


Figure 1. X-ray crystal structure of compound **4b**.

($R = C_6H_{11}$), led predominantly to the corresponding dioxabicyclo[2.2.2]octanes **4c**, **4d**, and **4f**, in 61%, 75%, and 60% chemical yields, respectively (Table 1, entries 7, 8, and 10).

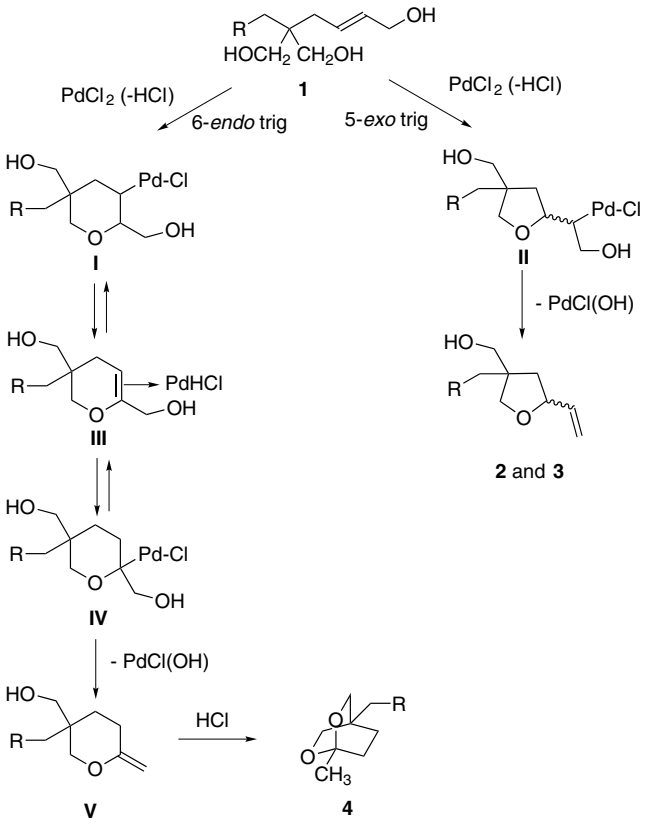
Cyclization of compound **1g** ($R = CH_3$) afforded the cyclized tetrahydrofurans **2g** and **3g** and the bicyclo-derivative **4g** in practically the same amounts (Table 1, entry 11), when cyclization of bishydroxy allylic alcohol **1e** (R = cinnamyl) gave the cyclized tetrahydrofurans **2e** and **3e** as the main products (75% yield), dioxabicyclo[2.2.2]octane **4e** being now the minor one (19% yield) (Table 1, entry 9). It is to be noticed that dioxabicyclo[2.2.2]octane **4e** was recently obtained via an $AuCl_3$-catalyzed cycloisomerization of a bis-homopropargylic diol.[9]

The cycloisomerization process was also extended to the bis-hydroxy allylic alcohol **1h**; tetrahydropyran derivatives **2h** and **3h** and dioxabicyclo[2.2.3]nonane **4h** were

obtained in a 3/1 ratio, tetrahydropyrans **2h** and **3h** being a 6:4 mixture of the two epimers (Table 1, entry 12).

A plausible mechanism for the Pd(II)-catalyzed cycloisomerization of these bis-hydroxy allylic alcohols is shown in Scheme 2. Addition of the oxygen and palladium to the double bond of compound **1** afforded the intermediate σ-palladium complex **I** via a 6-*endo*-trig cyclization, or the σ-palladium complex **II** via a 5-*exo*-trig cyclization. Subsequent elimination of PdCl(OH) from intermediate **II** gave the tetrahydrofuran epimers **2** and **3**. On the other hand, a β-H elimination from the σ-palladium complex **I** afforded the π-palladium complex **III**; hydropalladation of **III** led to the new σ-palladium complex **IV**. Subsequent elimination of PdCl(OH) afforded 2-methylenetetrahydrofuran **V**, whose cyclization to dioxabicyclo[2.2.2]octane **4** could be initiated by the catalytic amount of HCl formed in the reaction or by PdCl(OH). Such intramolecular oxypalladation of hydroxyalkenes leading to dioxabicyclo compounds has already been published.[10]

In summary, we have found that bis-hydroxy allylic alcohols undergo a quantitative palladium(II)-catalyzed intramolecular cyclization to provide a mixture of (3-alkyl-5-vinyltetrahydrofuran-3-yl)methanol and 4-alkyl-1-methyl-2,6-dioxabicyclo[2.2.2]octane. Work is currently in progress in order to find the conditions allowing the selective access to the tetrahydrofuran or the dioxabicyclo[2.2.2]octane structure.



Scheme 2.

Acknowledgments

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7. Representative procedure for the Pd(II)-catalyzed cyclization: A solution of $PdCl_2(CH_3CN)_2$ (5.2 mg, 0.02 mmol) in THF (3 mL) was added to a solution of alcohol **1** (0.4 mmol) in THF (3 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 24 h. The solvent was evaporated and the mixture was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent to afford compounds **2**, **3**, and **4**.
rac-(3*S**,5*S**)-(3-Benzyl-5-vinyltetrahydrofuran-3-yl)methanol **2a**: Colorless oil, R_f 0.24 (petroleum ether/diethyl ether 1/1); ^{1}H NMR ($CDCl_3$): δ 1.64 (dd, 1H, $J = 12.8$, 8.8 Hz, H-4), 1.85 (s, 1H, OH), 1.97 (dd, 1H, $J = 12.8$, 7.0 Hz, H-4), 2.78 (d, 1H, $J = 13.4$ Hz, $C_6H_5CH_2$), 2.88 (d, 1H, $J = 13.4$ Hz, $C_6H_5CH_2$), 3.48 (s, 2H, CH_2OH), 3.68 (d, 1H, $J = 8.9$ Hz, H-2), 3.77 (d, 1H, $J = 8.9$ Hz, H-2), 4.41 (ddd, 1H, $J = 8.8$, 7.0, 6.6 Hz, H-5), 5.10 (ddd, 1H, $J = 10.4$, 1.3, 1.3 Hz, CH=CH_2), 5.24 (ddd, 1H, $J = 17.0$, 1.3, 1.3 Hz, CH=CH_2), 5.86 (ddd, 1H, $J = 17.0$, 10.4, 6.6 Hz, CH=CH_2), 7.15–7.35 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 40.9, 40.9, 50.3, 65.5, 75.0, 80.3, 115.7, 126.8, 128.7, 130.3, 130.5, 138.6, 139.5.
rac-(3*R**,5*S**)-(Benzyl-5-vinyltetrahydrofuran-3-yl)methanol **3a**: Colorless oil, R_f 0.32 (petroleum ether/diethyl ether 1/1); ^{1}H NMR ($CDCl_3$): δ 1.48 (dd, 1H, $J = 13.0$, 8.3 Hz, H-4), 1.57 (s, 1H, OH), 2.07 (dd, 1H, $J = 13.0$, 7.5 Hz, H-4), 2.81 (d, 1H, $J = 13.4$ Hz, $C_6H_5CH_2$), 2.92 (d, 1H, $J = 13.4$ Hz, $C_6H_5CH_2$), 3.46 (d, 1H, $J = 10.5$ Hz, CH_2OH), 3.52 (d, 1H, $J = 10.5$ Hz, CH_2OH), 3.67 (d, 1H, $J = 8.9$ Hz, H-2), 3.83 (d, 1H, $J = 8.9$ Hz, H-2), 4.42 (ddd, 1H, $J = 8.3$, 7.5, 6.4 Hz, H-5), 5.12 (ddd, 1H, $J = 10.4$, 1.1, 1.1 Hz, CH=CH_2), 5.27 (ddd, 1H, $J = 17.0$, 1.1, 1.1 Hz, CH=CH_2), 5.88 (ddd, 1H, $J = 17.0$, 10.4, 6.4 Hz, CH=CH_2), 7.20–7.40 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 40.2, 40.9, 50.3, 66.9, 75.4, 80.3, 116.0, 126.8, 128.7, 130.3, 130.5, 139.2.
4-Benzyl-1-methyl-2,6-dioxabicyclo[2.2.2]octane **4a**: White solid, mp 78–80 °C, R_f 0.52 (petroleum ether/diethyl ether 1/1); ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.60–1.70 (m, 2H, CH_2), 1.85–1.96 (m, 2H, CH_2), 2.45 (s, 2H, $CH_2C_6H_5$), 3.78 (br d, 2H, $J = 8.1$ Hz, CH_2O), 3.89 (br d, 2H, $J = 8.1$ Hz, CH_2O), 6.97–7.33 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 25.5 , 28.3, 32.2, 33.2, 41.0, 73.3, 95.1, 127.0, 128.7, 130.3, 136.3.

8. Crystallographic data (CCDC) for **4b** have been deposited with the Cambridge Crystallographic Data Center with the register number CCDC 284729. These data can be obtained on request from The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk].
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