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Palladium-Catalyzed Stereospecific 1,4-Hydrogen Migration of *cis*-Cyclohex-2-en-1,4-diol Systems

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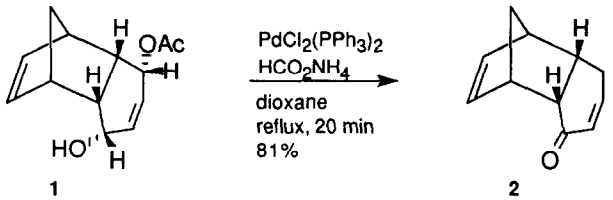
Abstract: It has been revealed that the generation of 2-cyclohexenones from *cis*-1,4-dihydroxycyclohexene derivatives under $PdCl_2(PPh_3)_2$-HCO_2NH_4 system takes place in an intramolecular pathway involving unprecedented mode of suprafacial 1,4-hydrogen migration across the 1,4-allylic centers.

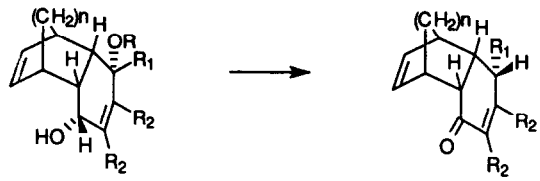
Recently, we disclosed a novel palladium-mediated reaction converting a mono-ester of a *cis*-1,4-dihydroxycyclohexene into a 2-cyclohexenone in one step in an excellent yield[1,2] in which we believed the formate hydrogen being incorporated into the product[3~5] (**Scheme 1**). The present investigation revealed that the reaction did not occur in the intermolecular pathway,[3~5] but in an unprecedented intramolecular suprafacial 1,4-hydrogen migration mechanism. We herein wish to present some evidences supporting the intramolecular mechanism.



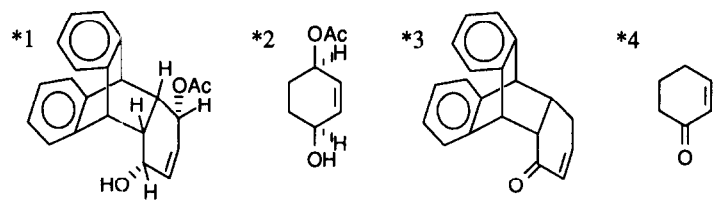
Scheme 1

We first examined generality of the reaction under various conditions (**Table 1**). The reaction takes place in the presence of a catalytic amount (1 mol%) of dichlorobis(triphenylphosphine)palladium (II) and 1.5 equiv. of ammonium formate to furnish the corresponding enones irrespective of the substituents on the double bond and 5,6-carbon atoms if 1,4-oxygens are in a *endo-cis*-relationship with at least one of which to be hydroxy. With the substrates having no hydroxy group, such as acetates, silyl ethers, methoxyethylmethyl ethers, the reaction does not occur at all remaining the starting materials unchanged. Interestingly, of three 1,4-*trans*-substrates having the same framework as **1**, only the *endo*-hydroxy:*exo*-acetoxy substrate furnished the enone (**2**) in 10% yield, while both of the *exo*-hydroxy:*endo*-acetoxy- and *trans*-1,4-dihydroxy substrates afforded the β,γ-unsaturated *exo*-cyclohexenol, in 72 and 32% yields, the latter of which could be apparently generated by the conventional hydrogenolysis mechanism.[3~5] As to the solvent, although the reaction takes place in both dioxane and acetonitrile, the latter is found to be more preferable presumably due to its simultaneous ligand

Table 1.[a] Conversion of the Cyclohexenol (**A**) into the Cyclohexenone (**B**)



Entry	substrate A				solvent[b]	time	product B		yield[c]
	R :	R_1 :	R_2	n		(min)	R_1 :	R_2	(%)
1	Ac :	H :	H	1	D	20	H :	H	81[d]
2	Ac :	H :	H	1	A	20	H :	H	77[d]
3	Ac :	H :	H	2	D	20	H :	H	84[d]
4	Ac :	H :	H	2	A	20	H :	H	79[d]
5	Piv :	H :	H	1	D	20	H :	H	79[d]
6	Piv :	H :	H	2	A	20	H :	H	79[d]
7	H :	H :	H	1	D	20	H :	H	trace
8	H :	H :	H	1	A	20	H :	H	72
9	H :	H :	H	2	A	20	H :	H	84
10	Ac :	H :	Me	1	A	20	H :	Me	65
11	Ac :	Me :	H	1	A	60	Me :	H	76
12	H :	Me :	H	1	A	150	Me :	H	65
13		*1			D	120	*3		69
14		*2			A	20	*4		42



a) The reaction was carried out by treating **A** in a solvent (10 ml/mmol) with $PdCl_2(PPh_3)_2$ (1 mol%) and HCO_2NH_4 (1.5 equiv.). b) A: acetonitrile and D: dioxane. c) Isolated yield after silica gel column chromatography. d) Optically pure substrate **A** was used. Preservation of the original chiral integrity was ascertained by hplc using a chiral column.

property, in which the diol substrate, being almost inert in the former solvent, reacts facilely to give the enones in a good yield (entries 7 and 8:**Table 1**). As to the catalytic system, we could not find any better one than $PdCl_2(PPh_3)_2$-HCO_2NH_4 among tested (**Table 2**). Although more than a stoichiometric amount of the formate is inevitable to complete the reaction with a catalytic amount of the palladium, an anomalous case was also present where the reaction proceeds more than the formate used (entry 3:**Table 2**).

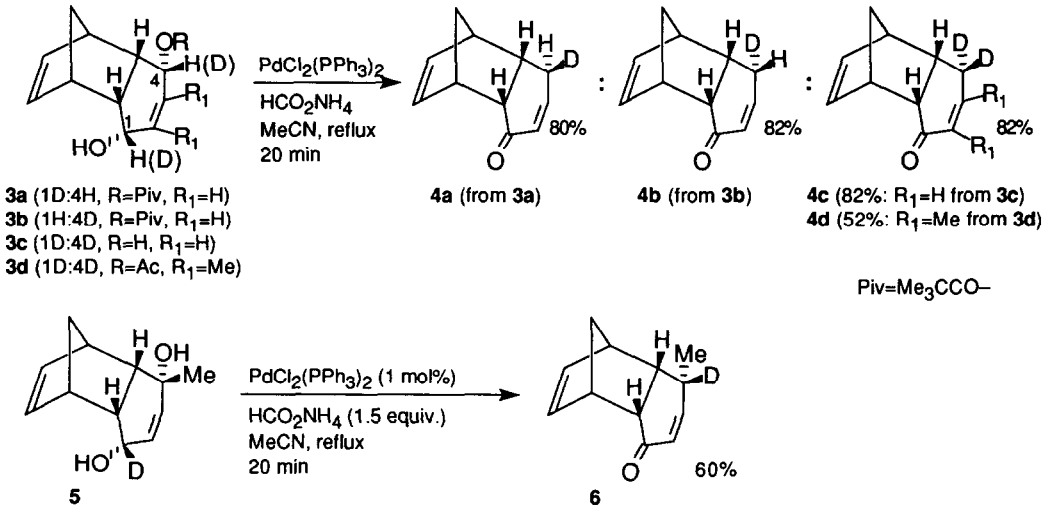
Particularly noteworthy in the present investigation is the deuterium labeling experiment shown in **Scheme 2**. This unambiguously demonstrated that the deuterium(hydrogen) atom on the C-1 center migrates

Table 2. Conversion of the Monoacetate (**1**) into the Cyclohexenone (**2**)

Entry	catalyst (mol%)	formate (mol)	solvent[a)]	time (min)	yield[b)] (%)
1	$PdCl_2(PPh_3)_2$ (100)	none	A	60	36
2	$PdCl_2(PPh_3)_2$ (1)	none	A	60	trace
3	$PdCl_2(PPh_3)_2$ (1)	HCO_2NH_4 (0.1)	A	30	41
4	$PdCl_2(PPh_3)_2$ (1)	HCO_2HEt_3N (1.5)	D	30	66
5	$Pd(PPh_3)_4$ (3)	none	A	60	trace
6	$Pd(PPh_3)_4$ (2)	HCO_2NH_4 (2.0)	D	60	none
7	$Pd(OAc)_2$ (2) + PPh_3 (10)	HCO_2NH_4 (2.0)	A	30	60

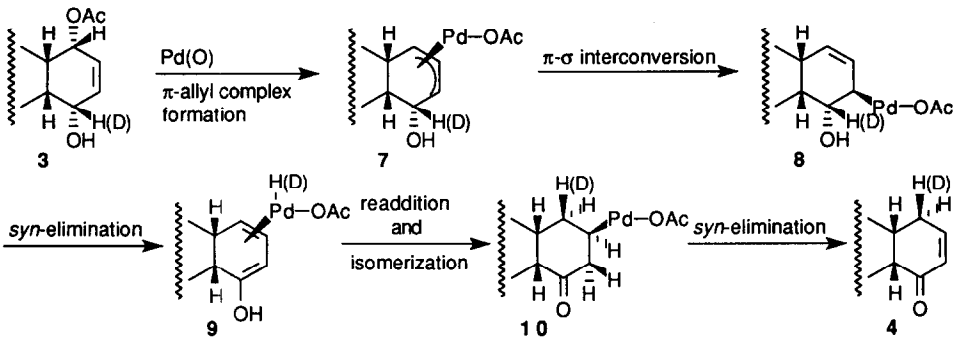
a) A: acetonitrile and B: dioxane. b) Isolated yield after silica gel column chromatography.

stereospecifically to the C-4 center from the same face to furnish the 4β-deuterio(hydro)enones with inversion of the stereochemistry of the C-4 center. It should be also noted that the inversion occurred in the 4-β-methyl analogue (**5**) with migration of 1-β-D(H) to afford the 4-α-methylenone (**6**) though the 1,4-di-β-methyl analogue did not give the 1,4-migration product. ^1H nmr as well as mass spectral analyses showed that neither a substantial loss nor scrambling of the deuterium atom contained in the substrates occurred under these conditions.[6,7]



Scheme 2

Although we are still unsatisfactory by the fact that the non-*endo*-hydroxy substrates such as the diacetate and the MOM-ether of **1** were not changed at all under the same conditions, the present reaction may be best explained as in **Scheme 3**.[8] Namely, the monoacetate (**3**) could be transformed into the enone (**4**) in one step by spontaneous the π-allyl complex formation (**7**), π-σ interconversion to **8**, *syn*-elimination generating the dienol complex (**9**), its regio-selective readdition from the less hindered direction followed by isomerization to **10**, and regio-selective *syn*-elimination of more acidic hydrogen in **10** (**Scheme 3**).



Scheme 3

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6. ^{1}H nmr (500 MHz) ($CDCl_3$): δ_H (**2**) 1.28 (d, 1H, *J* 8.4 Hz), 1.37 (dt, 1H, *J* 8.4, 1.9 Hz), 1.97 (ddd, 1H, *J* 20.6, 4.0, 2.6 Hz), 2.55 (dddd, 1H, *J* 20.6, 10.3, 4.1, 2.2 Hz), 2.71 (tt, 1H, *J* 9.9, 3.6 Hz), 2.85 (dd, 1H, *J* 9.9, 4.0 Hz), 2.98 (br s, 1H), 3.33 (br s, 1H), 5.81 (dt, 1H, *J* 10.3, 2.3 Hz), 6.04 (dd, 1H, *J* 5.9, 2.9 Hz), 6.61 (dt, 1H, *J* 10.3, 4.0 Hz); δ_H (**2a**) 1.30 (d, 1H, *J* 8.6 Hz), 1.38 (dt, 1H, *J* 8.6, 1.8 Hz), 1.95 (br dd, 1H, *J* 6.1, 3.1 Hz), 2.71 (m, 1H), 2.89 (dd, 1H, *J* 10.0, 4.1 Hz), 2.99 (br s, 1H), 3.34 (br s, 1H), 5.83 (dd, 1H, *J* 10.3, 2.5 Hz), 6.05 (dd, 1H, *J* 5.5, 3.1 Hz), 6.11 (dd, 1H, *J* 5.5, 3.0 Hz), 6.62 (dd, 1H, *J* 10.3, 4.2 Hz); δ_H (**2b**) 1.30 (br d, 1H, *J* 8.4 Hz), 1.38 (dt, 1H, *J* 8.4, 1.7 Hz), 2.53 (br ddd, 1H, *J* 10.5, 6.0, 2.6 Hz), 2.71 (td, 1H, *J* 10.3, 3.7 Hz), 2.87 (dd, 1H, *J* 9.9, 4.0 Hz), 2.99 (br s, 1H), 3.34 (br s, 1H), 5.82 (dd, 1H, *J* 10.3, 2.6 Hz), 6.05 (dd, 1H, *J* 5.8, 2.9 Hz), 6.10 (dd, 1H, *J* 5.8, 2.9 Hz), 6.62 (dd, 1H, *J* 10.3, 4.0 Hz); δ_H (**2c**) 1.30 (d, 1H, *J* 7.9 Hz), 1.39 (dt, 1H, *J* 8.5, 1.8 Hz), 2.71 (br d, 1H, *J* 10.0, 4.0 Hz), 2.87 (dd, 1H, *J* 9.8, 3.7 Hz), 3.00 (br s, 1H), 3.35 (br s, 1H), 5.84 (d, 1H, *J* 10.0, 4.0 Hz), 6.06 (dd, 1H, *J* 6.1, 3.1 Hz), 6.11 (dd, 1H, *J* 6.1, 3.1 Hz), 6.22 (d, 1H, *J* 9.8 Hz); δ_H (**4**) (non-deuteriorized) 1.33 (d, 1H, *J* 8.5 Hz), 1.40 (dt, 1H, *J* 7.9, 1.8 Hz), 1.69 (s, 3H), 1.78 (s, 3H), 1.97 (br d, 1H, *J* 19.5 Hz), 2.55 (dd, 1H, *J* 19.5, 10.4 Hz), 2.68 (tt, 1H, *J* 9.8, 3.7 Hz), 2.87 (dd, 1H, *J* 10.4, 3.7 Hz), 2.98 (br s, 1H), 3.34 (br s, 1H), 6.04 (dd, 1H, *J* 6.1, 3.1 Hz), 6.08 (dd, 1H, *J* 6.1, 3.1 Hz); δ_H (**4**) 1.32 (d, 1H, *J* 8.5 Hz), 1.39 (d, 1H, *J* 8.9 Hz), 1.69 (s, 3H), 1.78 (s, 3H), 2.64-2.72 (m, 1H), 2.86 (ddd, 1H, *J* 10.4, 3.7, 1.8 Hz), 2.98 (br s, 1H), 3.34 (br s, 1H), 6.04 (dd, *J* 6.1, 3.1 Hz), 6.08 (dd, *J* 6.1, 3.1 Hz); δ_H (**5**) (non-deuteriorized) 1.18 (d, 3H, *J* 7.7 Hz), 1.27 (br d, 1H, *J* 8.4 Hz), 1.37 (dt, 1H, *J* 8.4, 2.0 Hz), 2.68 (br td, 1H, *J* 3.7, 1.2 Hz), 2.74-4.82 (m, 1H), 2.99-3.18 (m, 2H), 3.33-3.35 (m, 1H), 5.73 (d, 1H, *J* 3.3 Hz), 5.76 (dd, 1H, *J* 6.2, 2.9 Hz), 6.0 (dd, 1H, *J* 6.2, 2.9 Hz), 6.34 (ddd, 1H, *J* 10.3, 2.5, 1.1 Hz); δ_H (**5**) 1.18 (s, 3H), 1.28 (br d, 1H, *J* 9.1 Hz), 1.38 (dt, 1H, *J* 8.6, 1.8 Hz), 2.69 (br d, 1H, *J* 9.2 Hz), 3.00-3.35 (m, 2H), 3.34-3.37 (m, 1H), 5.76 (d, 1H, *J* 10.4 Hz), 5.76 (dd, 1H, *J* 5.5, 3.1 Hz), 6.05 (dd, 1H, *J* 5.5, 2.4 Hz), 6.35 (d, 1H, *J* 10.3 Hz).
7. Loss of deuterium during the reaction could be estimated to be at most 5% which was determined by ^{1}H nmr spectra of the deuteriorized compounds, **2a~c**, **4** and **5**.
8. We thank a reviewer for suggesting us the present mechanism.

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