Regioselective Control in the Palladium-Catalyzed Isomerization of Methylenecyclopropylcarbinols Using Acetic Acid as a Reagent

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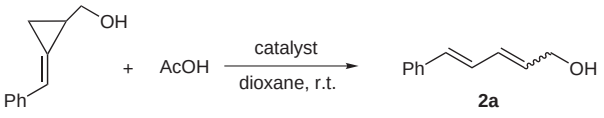
Abstract: Tuning the regioselectivity of the Pd-catalyzed isomerization of methylenecyclopropylcarbinols in acetic acid is achieved by a subtle choice of the ligand and/or solvent. When dioxane is used as the solvent, penta-2,4-dien-1-ols are formed, whereas when $AsPh_3$ is used as the ligand and toluene is used as the solvent, pent-4-enals are formed. A plausible reaction mechanism is discussed on the basis of the control experiments.

Key words: regioselectivity, palladium-catalyzed isomerization, methylenecyclopropylcarbinols, acetic acid

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that serve as useful building blocks in organic synthesis. MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force.[1] Transition-metal-catalyzed reactions (such as Pd, Rh, Ru, and Pt) of MCPs with various reactants have attracted much attention.[2] Recently, we reported Pd-catalyzed isomerization of MCPs in the presence of acetic acid at 80 °C in toluene to give the corresponding 1-substituted or 1,1-disubstituted dienes in good to excellent yields.[3] This result prompted us further to examine the Pd-catalyzed isomerization of another type of MCPs, methylenecyclopropylcarbinols **1** bearing an additional hydroxymethyl group.[4] During this examination, we found that the regioselectivity of this isomerization can be easily tuned by a subtle choice of the ligand and/or solvent. Namely, when dioxane is used as the solvent, penta-2,4-dien-1-ols[5] are formed in high yields, whereas when $AsPh_3$ is used as the ligand and toluene is used as the solvent, pent-4-enals[6] are formed in good yields. A plausible reaction mechanism is discussed on the basis of the control experiments.

The isomerization of 2-(phenylmethylene)cyclopropylcarbinol (*E*)-**1a** (0.4 mmol) was first carried out in the presence of acetic acid (0.16 mmol, 0.4 equiv) with various transition-metal catalysts (0.02 mmol) at room temperature in a variety of solvents to screen the best reaction conditions.[7] We found that $Pd(PPh_3)_4$ can effectively catalyze the isomerization of (*E*)-**1a** to give (*E*,*E*)-5-phenylpenta-2,4-dien-1-ol (**2a**) in high yield as a major isomer (*E*,*E*:*Z*,*E* = 93:7) in 1,4-dioxane (Table 1, entry 1). $Pd(OAc)_2$ is not as effective as $Pd(PPh_3)_4$ under identical conditions (Table 1, entry 2). $PdCl_2(PPh_3)_2$, $Pd(dba)_2$, $Ru_3(CO)_{12}$ and $NiCl_2(dppe)$ did not catalyze this reaction (Table 1, entries 3–6). The best reaction conditions for this transformation are to carry out the reaction in the presence of acetic acid (0.4 equiv) and $Pd(PPh_3)_4$ (5 mol%) in dioxane at room temperature. Under these optimized conditions, we next examined a variety of methylenecyclopropylcarbinols (*E*)-**1** for this transformation. The results are summarized in Table 2. The corresponding isomerized products (*E*,*E*)-penta-2,4-dien-1-ols **2** were obtained in high yields within 11–15 hours as major isomers in most cases (Table 2).

Table 1 Isomerization of 2-(Phenylmethylene)cyclopropylcarbinol (*E*)-**1a** by a Variety of Catalysts in the Presence of Acetic Acid in Dioxane



(*E*)-**1a** **2a**

Entry[a]	Catalyst	Time (h)	Yield (%)[b] **2a** (*E*,*E*:*Z*,*E*)[c]
1	$Pd(PPh_3)_4$	12	90 (93:7)
2	$Pd(OAc)_2$	11	50 (93:7)[d]
3	$PdCl_2(PPh_3)_2$	13	n.r.[d]
4	$Pd(dba)_2$	12	n.r.
5	$Ru_3(CO)_{12}$	12	n.r.
6	$NiCl_2(dppe)$	12	n.r.

[a] Reaction conditions: (*E*)-**1a** (0.4 mmol), AcOH (0.16 mmol), catalyst (0.02 mmol), dioxane (2.0 mL).
[b] Isolated yields.
[c] Determined by analysis of ^1H NMR spectroscopic data.
[d] PPh_3 (0.16 mmol) was added.

Interestingly, when 2-(phenylmethylene)cyclopropylcarbinol (*E*)-**1a** (0.4 mmol) was treated with $Pd(PPh_3)_4$ (0.02 mmol) in the presence of acetic acid (0.4 mmol, 1.0 equiv) at 80 °C in toluene, (*E*)-5-phenylpent-4-enal (**3a)** was obtained in 62% yield along with a trace of **2a** (Table 3, entry 1). $Pd(dba)_2$, $Pd(PPh_3)_4$, and $Ru_3(CO)_{12}$ can also catalyze this isomerization under identical conditions, but give **3a** in lower yields (Table 3, entries 2–4). On the other hand, $PdCl_2(MeCN)_2$, $RuCl_2(PPh_3)_4$, $NiCl_2(dppe)$, and

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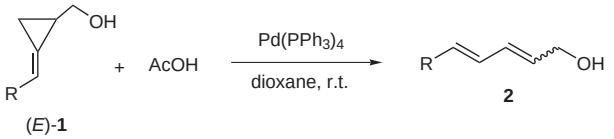
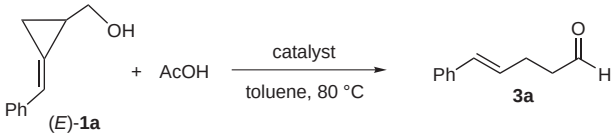
Table 2 Pd-Catalyzed Isomerization of a Variety of Methylenecyclopropylcarbinols (*E*)-**1** in Dioxane in the Presence of Acetic Acid



Entry[a]	(*E*)-**1** (*R*)	Time (h)	Yield (%)[b] **2** (*E*,*E*:*Z*,*E*)[c]
1	(*E*)-**1a** (Ph)	12	**2a**, 90 (93:7)
2	(*E*)-**1b** (4-FC_6H_4)	11	**2b**, 86 (96:4)
3	(*E*)-**1c** (4-ClC_6H_4)	11	**2c**, 84 (98:2)
4	(*E*)-**1d** (2-ClC_6H_4)	15	**2d**, 91 (94:6)
5	(*E*)-**1e** (4-BrC_6H_4)	11	**2e**, 92 (98:2)
6	(*E*)-**1f** (4-MeC_6H_4)	12	**2f**, 87 (96:4)
7	(*E*)-**1g** (4-$MeOC_6H_4$)	12	**2g**, 91 (98:2)
8	(*E*)-**1h** [3,4,5-$(MeO)_3C_6H_2$]	12	**2h**, 93 (96:4)
9	(*E*)-**1i** ($PhCH_2CH_2$)	12	**2i**, 90 (94:6)

[a] Reaction conditions: (*E*)-**1** (0.4 mmol), AcOH (0.16 mmol), $Pd(PPh_3)_4$ (0.02 mmol), dioxane (2.0 mL).
[b] Isolated yields.
[c] Determined by analysis of ^1H NMR spectroscopic data.

Table 3 Isomerization of 2-(Phenylmethylene)cyclopropylcarbinol (*E*)-**1a** in a Variety of Catalysts in the Presence of Acetic Acid in Toluene

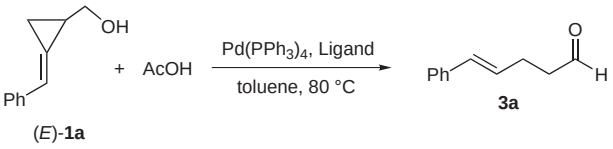


Entry[a]	Catalyst	Time (h)	Yield (%)[b] **3a**
1	$Pd(PPh_3)_4$	2	62[c]
2	$Pd(dba)_2$	10	30
3	$RuCl_2(PPh_3)_4$	10	25
4	$Ru_3(CO)_{12}$	10	5
5	$PdCl_2(MeCN)_2$	24	n.r.
6	$PdCl2(PPh_3)_2$	24	n.r.
7	$NiCl_2$(dppe)	24	n.r.
8	$Ni(acac)_2$	24	n.r.

[a] Reaction conditions: (*E*)-**1a** (0.4 mmol), AcOH (0.4 mmol), catalyst (0.02 mmol), toluene (2.0 mL).
[b] Isolated yields.
[c] PPh_3 (0.16 mmol) was added.

$Ni(acac)_2$ did not catalyze this isomerization under identical conditions (Table 3, entries 5–8).

Table 4 Ligand Screening for the Pd-Catalyzed Isomerization of 2-(Phenylmethylene)cyclopropylcarbinol (*E*)-**1a** in the Presence of Acetic Acid in Toluene



Entry[a]	Ligand	Time (h)	Yield (%)[b] **3a**
1	–	3	63
2	$AsPh_3$	2	83
3	TFP	2	81
4	PPh_3	2	62
5	PBu_3	6	58
6	DPE-Phos	3	55
7	dppp	12	50
8	dppb	12	40
9	bipyridine	4	40
10	$P(OPh)_3$	18	20
11	$Pd(dba)_2$ + $AsPh_3$	15	59[c]
12	$Pd(OAc)_2$ + $AsPh_3$	15	19

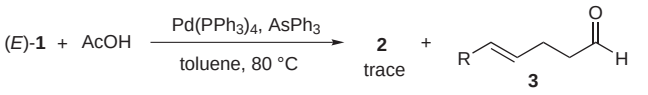
[a] Reaction conditions: (*E*)-**1a** (0.4 mmol), AcOH (0.4 mmol), $Pd(PPh_3)_4$ (0.02 mmol), ligand (0.16 mmol), toluene (2.0 mL).
[b] Isolated yields.
[c] Compound **3a** was obtained with a small amount of dba.

To improve the yield of **3a**, the isomerization of 2-(phenylmethylene)cyclopropylcarbinol [(*E*)-**1a**] was carried out in the presence of acetic acid and $Pd(PPh_3)_4$ with various ligands and a variety of solvents. As can be seen from Table 4, **3a** was obtained in good yield with $AsPh_3$ or TFP [tri(2-furyl)phosphine] as a ligand in toluene.[7] Considering the stability and cost of these two ligands, we next carried out this transformation in the presence of acetic acid (1.0 equiv), $Pd(PPh_3)_4$ (5 mol%) and $AsPh_3$ (0.4 equiv) in toluene at 80 °C. The results are summarized in Table 5. The corresponding pent-4-enals **3** were obtained in moderate to high yields within 1.5–12 hours for a variety of methylenecyclopropylcarbinols (*E*)-**1** along with a trace of penta-2,4-dien-1-ols **2** (Table 5). Using alkylidenecyclopropylcarbinol (*E*)-**1i** as the substrate, the corresponding product **3i** can be also obtained in 30% yield though in moderate conversion (Table 5, entry 8).

Their structures are determined by spectroscopic data, microanalyses and HRMS. The control experiment indicated that **3a** is not derived from the Pd(0)-catalyzed isomerization of **2a** under the standard conditions (Scheme 1).

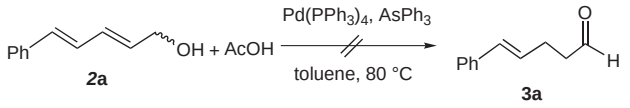
The mechanism of this highly regioselective Pd-catalyzed isomerization of methylenecyclopropylcarbinols (*E*)-**1** has not been unequivocally established, but one plausible

Table 5 Pd-Catalyzed Isomerization of a Variety of Methylenecyclopropylcarbinols (*E*)-**1** in Toluene in the Presence of Acetic Acid



Entry[a]	(*E*)-**1** (*R*)	Time (h)	Yield (%)[b] **3**
1	(*E*)-**1a** (Ph)	2	**3a**, 83
2	(*E*)-**1b** (4-FC_6H_4)	2	**3b**, 79
3	(*E*)-**1c** (4-ClC_6H_4)	1.5	**3c**, 78
4	(*E*)-**1d** (2-ClC_6H_4)	1.5	**3d**, 75
5	(*E*)-**1f** (4-MeC_6H_4)	5	**3f**, 66
6	(*E*)-**1g** (4-$MeOC_6H_4$)	3	**3g**, 90
7	(*E*)-**1h** [3,4,5-$(MeO)_3C_6H_2$]	5	**3h**, 70
8	(*E*)-**1i** ($PhCH_2CH_2$)	12	**3i**, 30[c]

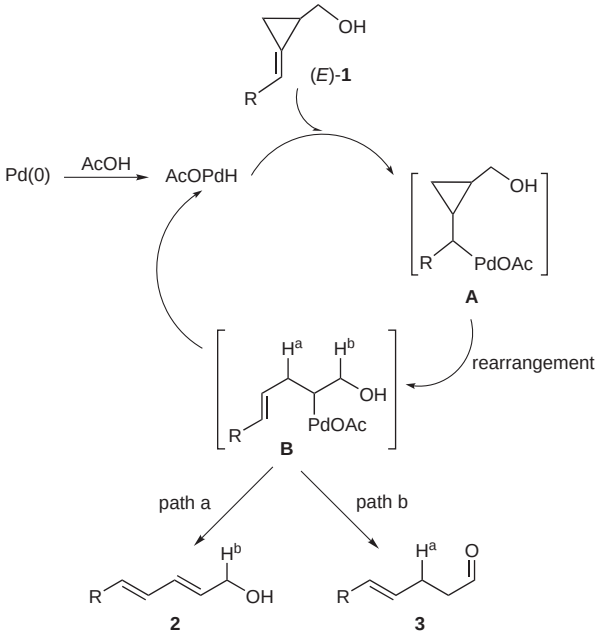
[a] Reaction conditions: (*E*)-**1** (0.4 mmol), AcOH (0.4 mmol), $Pd(PPh_3)_4$ (0.02 mmol), $AsPh_3$ (0.16 mmol).
[b] Isolated yields.
[c] The mixture was stirred at 65 °C and the starting material was recovered in 30% yield.



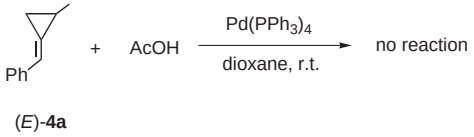
Scheme 1 Control experiment. *Reaction conditions*: **2a** (0.2 mmol), AcOH (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol), $AsPh_3$ (0.08 mmol), toluene (1.0 mL).

explanation is proposed in Scheme 2 based on the previous investigations[1,3,8,9] and above experimental observations. The initial step of this isomerization reaction is the hydropalladation of the double bond in methylenecyclopropylcarbinols (*E*)-**1** with the hydridopalladium species (H–Pd–OAc), generated from Pd^0 catalyst and acetic acid, to form the cyclopropylcarbinylpalladium complex **A**. The cyclopropylcarbinylpalladium to homoallylpalladium rearrangement leads to the formation of the species **B**. The subsequent β-hydride elimination (Pd–H) produces either product **2** (path a: via Pd–H_a elimination) or product **3** (path b: via Pd–H_b elimination) in two different orientations. The precoordinative solvent dioxane or the $AsPh_3$ ligand might be able to stabilize the reaction intermediate **A** or **B** to give the corresponding product **2** or **3** in good yield.

The control experiment shown in Scheme 3 suggests that the hydroxy group in 2-(arylmethylene)cyclopropylcarbinols **1** is important in this palladium-catalyzed isomerization of 2-(arylmethylene)cyclopropylcarbinols **1** because no reaction occurred using MCP (*E*)-**4a** as substrate under identical conditions. This may be due to that the hydroxyl group in intermediate **B** can coordinate to Pd center to stabilize this key species and therefore, provide a thermodynamic driving force for this Pd-catalyzed reaction.



Scheme 2 Proposed mechanism



Scheme 3 Palladium-catalyzed isomerization of MCP (*E*)-**4a** in the presence of acetic acid in dioxane

In conclusion, we have disclosed a highly regioselective Pd-catalyzed isomerization of methylenecyclopropylcarbinols (*E*)-**1** in the presence of acetic acid. By a subtle choice of ligand and/or solvent, the corresponding penta-2,4-dien-1-ols **2** and pent-4-enals **3** can be obtained in good to excellent yields. The mechanism has been discussed on the basis of the experimental observations and the control experiments. Further mechanistic investigations will be carried out by deuterium labeling experiments as well as DFT calculations. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

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(7) Solvent effects have been omitted due to the limited space of a communication, but are available from the authors upon request.

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