Highly Regioselective Palladium-catalyzed Double Hydroselenation of Terminal Alkynes with Benzeneselenol in the Presence of Acetic Acid

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(Received July 9, 2013; CL-130641; E-mail: ogawa@chem.osakafu-u.ac.jp)

Palladium diacetate $(Pd(OAc)_2)$, in the presence of acetic acid, is found to exhibit excellent catalytic activity for the double hydroselenation of terminal alkynes with benzeneselenol to yield the corresponding diselenoketals regioselectively.

Selenols are representative parent selenium molecules for the synthesis of various organoselenium compounds via nucleophilic substitution, addition, and oxidation.¹ In particular, addition to carbon-carbon unsaturated bonds is one of the most important methods for the synthesis of alkyl, vinyl, and allyl selenides: jonic addition and radical addition are usually employed for this purpose. Although the transition-metalcatalyzed addition of heteroatom compounds to alkynes, alkenes, and allenes is applicable to a series of heteroatom compounds, few examples of such reactions have been reported for organoselenium compounds.² This is likely attributable to the widespread belief that organoselenium compounds are representative catalyst poisons. Indeed, compared with organosulfur compounds, the transition-metal-catalyzed addition of organoselenium compounds, especially selenols, is a class of reactions that is difficult to achieve efficiently. This inefficiency is probably caused by the formation of a selenium-bridge between the metal atoms, leading to the formation of metal selenide aggregates that are not soluble in conventional organic solvents. Recently, however, our study group and others have developed a series of transition-metal-catalyzed addition of selenols to alkynes and allenes.³ For example, Pd(OAc)₂ with pyridine efficiently catalyzes the Markovnikov addition of selenols to terminal alkynes,^{3a} and [PdCl₂(PPh₃)₂]-catalyzed hydroselenation selectively proceeds via the Markovnikov addition and double bond isomerization (Scheme 1).3f

The success of these palladium-catalyzed addition reactions of selenols to alkynes is based on controlling the suppression of palladium selenide aggregates via coordination with excess amounts of alkynes. Very recently, we have developed the palladium-catalyzed double hydrothiolation of terminal alkynes with two equivalents of thiols to afford the corresponding



Scheme 1. Regioselective hydroselenation of terminal alkynes.

dithioketals regioselectively.⁴ In the case of the double hydroselenation of alkynes with selenols, the use of excess amounts of selenols compared with alkynes is presumed to cause metal selenide aggregation efficiently. Therefore, catalytic double hydroselenation is more difficult to achieve than the corresponding double thiolation. To achieve the catalytic double addition of selenols to alkynes, the reaction conditions for the desired double hydroselenation of alkynes using excess amounts of selenols have been investigated in detail.

The palladium-catalyzed double hydroselenation of 1-octyne with benzeneselenol was conducted under several reaction conditions, and the results are shown in Table 1. As the previously reported double hydrothiolation of terminal alkynes with thiols was conducted using $Pd(OAc)_2$ as a catalyst, THF as solvent, and H_2O as an additive, similar conditions were employed for the double hydroselenation (Entry 1). When the

 Table 1. Palladium-catalyzed double hydroselenation of 1-octyne^a

nulay		catalyst (5 mol%) additive (1 equiv)	PhSe SePh	ⁿ Pen	SePh
nex—	12 2	solvent (0.05 mL)	⁻ ⁿ Hex ⁻ +	1 011 32	12
	10 2	40 °C, 20 h	54		70
Entry	Catalvet	Additive	Solvent	Yield/% ^b	
Linuy	Catalyst	Additive	Solvent	5a	4a ^c
1	Pd(OAc) ₂	H_2O	THF	57	20
2	$Pd(OAc)_2$	AcOH	THF	(73)	0
3	$Pd(OAc)_2$	PhOH	THF	73	6
4	$Pd(OAc)_2$	MeOH	THF	31	6
5	$Pd(OAc)_2$	HCl ^d	THF	67	16
6	$Pd(OAc)_2$	H_2SO_4	THF	0	0
7	$Pd(OAc)_2$	<i>p</i> -TsOH	THF	0	0
8	$Pd(OAc)_2$	AcOH	acetone	49	12
9	$Pd(OAc)_2$	AcOH	EtOH	53	7
10	$Pd(OAc)_2$	AcOH	MeCN	55	12
11	$Pd(OAc)_2$	AcOH	CHCl ₃	60	0
12	$Pd(OAc)_2$	AcOH	benzene	53	8
13	$Pd(OAc)_2$	AcOH	Et ₂ O	67	7
14	$Pd(OAc)_2$	AcOH	1,4-dioxane	49	8
15	[PdCl ₂ (PPh ₃) ₂] AcOH	THF	7	24
16	[PdCl ₂ (PhCl	N) ₂] AcOH	THF	0	15
17	$[Pd_2(dba)_2]$	AcOH	THF	56	5
18	$[Pd(PPh_3)_4]$	AcOH	THF	7	23
19	[Pt(PPh ₃) ₄]	AcOH	THF	0	19

^a1-Octyne (0.1 mmol), PhSeH (0.2 mmol). ^bDetermined by ¹H NMR. Value in parenthesis is isolated yield. ^cObtained as a E/Z mixture (ca. 1:1). ^dAqueous HCl (12 M) was used.

Pd(OAc)₂-catalyzed reaction of 1-octyne (1a, 0.1 mmol) with two equivalents of benzeneselenol (2) was conducted in the presence of H₂O (1 equiv) in THF at 40 °C for 20 h, the double hydroselenation of 1-octyne proceeded regioselectively to afford the desired diselenoketal 5a in 57% yield along with vinyl selenide 4a (which was formed by the sequential Markovnikov addition and double bond isomerization). Changing the additive from H₂O to AcOH led to the selective formation of the desired 3a (Entry 2). PhOH and HCl were also effective for double hydroselenation, but only small amounts of 4a were formed concomitantly (Entries 3 and 5). Strong acids such as H₂SO₄ and p-TsOH inhibited hydroselenation, probably because the catalyst was decomposed (Entries 6 and 7). Next, we examined double hydroselenation using AcOH as an additive by varying the solvents (Entries 8-14). Double hydroselenation proceeded in a variety of solvents such as nonpolar-aprotic solvent (benzene [empirical solvent parameter E_T^N : 0.111], Et₂O [0.117], 1,4dioxane [0.164], THF [0.207], CHCl₃ [0.259]), polar-aprotic solvent (acetone [0.355], MeCN [0.460]), and protic solvent (EtOH [0.654]).⁵ Among these, THF showed the best results. Therefore, we next focused on double hydroselenation using AcOH as an additive and THF as a solvent in the presence of several transition-metal catalysts (Entries 15-19). Double hydroselenation was found to be very sensitive to the catalyst used. Palladium chloride derivatives were ineffective for double hydroselenation, although monohydroselenation proceeded to afford vinyl selenide 4a in low yields. [Pd2(dba)2] showed catalytic activity for double selenation. However, zero-valent palladium and platinum complexes were ineffective.

Table 2 shows the results of the palladium-catalyzed double hydroselenation of terminal alkynes with benzeneselenol under the optimized reaction conditions (Table 1, Entry 2).⁶ The carboxylic group and chloro group tolerate double hydroselenation, and the corresponding diselenoketals 5b and 5c were obtained in moderate to good yields (Entries 2 and 3). Propargyl ether 1d also afforded the corresponding diselenoketal 5d in fair yield (Entry 4). Aromatic alkynes such as phenylacetylene regioselectively afforded diselenoketal 5e in moderate yield (Entry 5). The formed diselenoketals 5 are synthetically useful because they can be easily transferred to α -selenoanion species upon treatment with butyllithium.¹ In the absence of AcOH, the yield of the double hydroselenation products decreased. For example, the double hydroselenation of 1c afforded 61% of 5c, whereas only a trace amount of diselenoketal 5d was obtained. Moreover, the Pd(OAc)₂-catalyzed reaction of 1b in the absence of AcOH yielded 5% of 5b along with its cyclization product (48%, y-(phenylseleno)-y-valerolactone) formed via intramolecular cyclization with elimination of PhSeH. The present double hydroselenation can be applied to alkyne 1f having a ferrocenyl group. The Pd(OAc)2-catalyzed reactions of 1f with PhSeH in the presence and absence of AcOH afforded the corresponding diselenoketal 5f in 33% and 73% vields. respectively without any decomposition of the ferrocenyl group (Entry 6). The structure of 5f was unambiguously determined by X-ray crystal analysis (see Supporting Information). In general, aromatic diselenoketals (ArC(SePh)2R) are known to be unstable in the presence of selenols and undergo reduction to give the corresponding selenides (ArCH(SePh)R).^{7,8} Accordingly, in the case of 1f, the presence of AcOH accelerates the reduction to FcCH(SePh)CH₃, resulting in decrease in the yield of 5f.

 Table 2. Palladium-catalyzed double hydroselenation of alkynes^a

R-==	+ PhSeH	_	Pd(OAc) ₂ (5 mol%) AcOH (1 equiv)	PhSe SePh	
1	2		1111, 40 0, 2011	5	
Entry	Alkyne		Yield/% ⁵		
1	ⁿ Hex—	1a	PhSe SePh ⁿ Hex	5a	80 (73)
2 HO ₂		1b	PhSe SePh HO ₂ C	5b	59
3 CI	<u> </u>	1c	PhSe SePh	5c	(87)
4	MeO	1d	PhSe SePh MeO	5d	(34)
5	Ph-===	1e	PhSe SePh Ph	5e	32
6 ^c	Fe S	1f	PhSe SePh Fe	5f	73

^aAlkyne (0.5 mmol), PhSeH (1.0 mmol), THF (2.0 M). ^bDetermined by ¹H NMR. Values in parenthesis are isolated yield. ^cIn the absence of AcOH, Pd(OAc)₂ (2 mol%), THF, 40 °C, 16 h.

Tabl	le 3	. F	Iydrose	lenation	of	vinyl	selenide	3a	with	PhSeH ^a
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S	ePh	catalyst (5 additive (7	PhSe_SePh	
ⁿ Hex	+ PhSeH	THF (2 M)), 40 °C	ⁿ Hex
3a	2			5a
Entry	Catalyst	Additive	Time/h	Yield/% ^b
1	none	none	20	NR ^c
2	none	AcOH	20	NR ^c
3	$Pd(OAc)_2$	none	10	45
4	$Pd(OAc)_2$	none	20	72
5	$Pd(OAc)_2$	AcOH	10	50
6	Pd(OAc) ₂	AcOH	20	79

^aVinyl selenide **3a** (0.2 mmol), PhSeH (0.2 mmol). ^bDetermined by ¹H NMR. ^cNo reaction.

To obtain further information about the mechanistic pathways of the double hydroselenation reaction, we examined the reaction of vinyl selenide 3a, as a monohydroselenation product, with PhSeH under various reaction conditions; the results of the same are summarized in Table 3.

In the absence of palladium catalyst, the addition of PhSeH to **3a** did not proceed even in the presence of acetic acid (Entries 1 and 2). When Pd(OAc)₂ was used in the absence of AcOH, hydroselenation of **3a** gradually proceeded to afford diselenoketal **5a** in 45% yield for 10 h and in 72% yield for 20 h (Entries 3 and 4, respectively). The use of AcOH in the presence of Pd(OAc)₂ somewhat accelerated the hydroselenation of **3a** (Entries 5 and 6). These results clearly indicate that the second hydroselenation (i.e., hydroselenation of **3a**) requires a palla-



Scheme 2. A possible pathway for double hydroselenation of terminal alkynes.

dium catalyst; AcOH is not essential for this process. Accordingly, the first hydroselenation (i.e., hydroselenation of terminal alkyne) requires both $Pd(OAc)_2$ and AcOH when excess amounts of PhSeH relative to the alkyne are employed.

A possible pathway for the present palladium-catalyzed double hydroselenation of terminal alkynes is shown in Scheme 2. Palladium diacetate undergoes a ligand-exchange reaction with two equivalents of benzeneselenol to afford palladium diselenide A.⁹ Then, the selenopalladation of the terminal alkynes occurs regioselectively to form vinylpalladium intermediates **B**, the protonolysis of which with benzeneselenol (and/or acetic acid) affords vinyl selenides **3** with the recovery of palladium selenides **A**. The formed vinyl selenides **3** undergo further addition of benzeneselenol in the presence of palladium catalyst to afford diselenoketals **5**. If the palladium selenide **A** aggregates to form a polymeric structure, it loses its catalytic activity. Therefore, AcOH may act not only as a proton source for **B** but also as an inhibitor for the aggregation of **A**.

In summary, we have developed a highly regioselective double hydroselenation of terminal alkynes with two equivalents of benzeneselenol. The mechanistic details of the double hydroselenation and its application to the development of the transition-metal-catalyzed reactions of other selenium compounds are now under investigation.

This work was supported in part by a Grant-in-Aid for Scientific Research for JSPS Fellows (No. 2510638). T.T. thanks the Japan Society for the Promotion of Science for the Research Fellowship for Young Scientists.

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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- General procedure: In a two-necked 10-mL flask with a 6 magnetic stirring bar under N2 atmosphere were placed Pd(OAc)₂ (0.025 mmol), freshly distilled THF (0.25 mL), 1-octyne (0.5 mmol), benzeneselenol (0.2 mmol), and acetic acid (0.1 mmol) in that order. The reaction was conducted at 40 °C for 20 h, and then the resulting solution was filtered through Celite with ethyl acetate as an eluent. Concentration in vacuo, and purification by preparative TLC (silica gel, eluent: hexane) provided 2,2-bis(phenylselanyl)octane (5a) [103971-60-4]: Slight yellow oil; ¹HNMR (400 MHz, CDCl₃): δ 0.88 (t, 3H, J = 8.0 Hz), 1.23–1.30 (m, 6H), 1.37 (quint, 5H), 1.75-1.79 (m, 2H), 7.22-7.38 (m, 6H), 7.66–7.68 (m, 4H); 13 C NMR (100 MHz, CDCl₃): δ 14.0, 22.5, 24.7, 28.1, 29.2, 31.7, 41.5, 64.2, 128.4, 128.9, 132.1, 136.8; ⁷⁷Se NMR (75 MHz, CDCl₃): δ 508.1; IR (NaCl): 3055, 2955, 2928, 2855, 1577, 1474, 1435, 1369, 1300, 1180, 1119, 1049, 1022, 999, 914, 740, $690 \,\mathrm{cm}^{-1}$. The selected spectral and analytical data for the double hydroselenation products, 5b, 5c, 5d, and 5f are shown in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www. csj.jp/journals/chem-lett/index.html.
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- 8 The formation of reduction products, selenides, was confirmed by NMR spectroscopy. For example, spectral data of reduction product of **5e** are shown in below. ¹H NMR (400 MHz, CDCl₃): δ 1.75 (t, 3H, J = 6.9 Hz), 4.56 (q, J = 6.9 Hz, 1H), 7.17–7.29 (m, 8H), 7.42–7.45 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 22.3, 42.6, 127.0, 127.3, 127.9, 128.4, 128.9, 129.9, 135.5, 143.7.
- 9 In our previous paper, we described that the reaction of Pd(OAc)₂ with 2 equivalents of PhSeH led to the formation of palladium selenide complex and AcOH: see ref 3b.