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Palladium-Catalyzed Dienylation of Haloalkynes using 2,3-Butadienyl Acetates: A Facile Access to (1Z)-1,2-Dihalo-3-vinyl-1,3-dienes

Dongxu Chen,^a Xiaoyi Chen,^a Zenghui Lu,^a Haiting Cai,^a Jinbei Shen,^a and Gangguo Zhu^{a,b,*}

^a Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, People's Republic of China Fax: (+86)-579-8228-2610; phone: (+86)-579-8228-3702; e-mail: gangguo@zjnu.cn

^b Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, Zhejiang Normal University, Jinhua 321004, People's Republic of China

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Abstract: A highly efficient and stereoselective method for the synthesis of (1Z)-1,2-dihalo-3-vinyl-1,3-dienes featuring palladium-catalyzed coupling of haloalkynes and 2,3-butadienyl acetates was developed. The resulting products were smoothly converted into *cis*-1,2-dihalostyrene derivatives using the Diels–Alder/aromatization sequence.

Keywords: alkynes; C–C bond formation; dienes; halopalladation; palladium

Transition metal-catalyzed reactions have become powerful tools for the formation of carbon-carbon and carbon-heteroatom bonds in organic synthesis.^[1] In this regard, the halopalladation reaction of acetylenes has attracted considerable attention over the past decades, owing to its easy access to highly functionalized haloalkenes in a rather efficient and atomeconomical way.^[2-4] Despite the significant progress that has been achieved along this line, the halopalladation reaction was mainly limited to the addition of allyl halides, carbon monoxide and 1,3-dienes. Therefore, an exploration of the trapping of alkenyl-palladium intermediates resulting from halopalladation of the C=C triple bond with other readily available materials, such as allyl alcohol or 2,3-butadienol, is still highly desirable.

In 2006, Jiang and co-workers^[4a] disclosed an elegant protocol for the stereoselective approach to 1,4dienes through Pd-catalyzed coupling of alkynes with allyl alcohol. Li's group^[5] also implemented a series of halopalladation-initiated annulation reactions by the use of intramolecular nucleophiles, such as hydroxy, amine, and more recently, carbon nucleophiles as the capture reagents.

Very recently, we^[6] reported a convenient method for the regio- and stereoselective synthesis of (1Z)- or (1E)-1,2-dihalo-1,4-dienes with the halopalladation of haloalkynes as the key step. In a subsequent study of the haloallylation of alkynyl halides with allyl alcohol, we found that phenylethynyl bromide (**1a**) was selectively allylated to give **2a** in 81% yield, whereas phenylacetylene was intact under the reaction conditions (Scheme 1).

The unique reactivity of haloalkynes under the halopalladation conditions promoted us to examine the feasibility of trapping the alkenyl-palladium intermediate with readily accessible substrates, such as 2,3butadienol and its derivatives, for diversity-oriented synthesis (DOS).^[7] Herein, we report the Pd-catalyzed dienylation reaction of haloalkynes with 2,3-butadienyl acetates as the capture reagents, allowing access to (1*Z*)-1,2-dihalo-3-vinyl-1,3-dienes in a highly efficient and stereoselective fashion.

In the initial attempts to achieve the dienylation of haloalkynes, we found that treatment of phenylethynyl bromide (**1a**) and 2,3-butadienol (**3a**) in the presence of 5 mol% of Pd(OAc)₂ and 2 equivalents of LiBr in HOAc at 60 °C gave the desired 1,2-dibromo-3-vinyl-1,3-diene **4aa** in 58% yield with 82:18 mixture



Scheme 1. Competitive reaction of 1a and phenylacetylene.

Table 1. Optimization of the reaction conditions.^[a]



Entry	3/ X	PdL _n	Solvent	Yield [%] ^[b,c]	Z/E ^[d]
1	3a /OH	$Pd(OAc)_2$	HOAc	58	82/18
2	3b/OBz	$Pd(OAc)_2$	HOAc	62	87/13
3	3c/ Br	$Pd(OAc)_2$	HOAc	21	81/19
4	3d/OAc	$Pd(OAc)_2$	HOAc	78	84/16
5	3d/OAc	$Pd(OAc)_2$	DMSO	trace	_
6	3d/OAc	$Pd(OAc)_2$	DMF	trace	_
7	3d/OAc	$Pd(OAc)_2$	THF	82	90/10
8	3d/OAc	$Pd(OAc)_2$	dioxane	86	91/9
9	3d/OAc	$Pd(OAc)_2$	CH ₃ CN	90(85) ^[c]	>95/5
10	3d/OAc	PdCl ₂	CH ₃ CN	79	91/9
11	3d/OAc	PdBr ₂	CH ₃ CN	80	93/7
12	3d/OAc	$Pd(MeCN)_2Cl_2$	CH ₃ CN	83	92/8
13	3d/OAc	$Pd(PhCN)_2Cl_2$	CH ₃ CN	77	91/9

[a] Reaction conditions: 1a (0.5 mmol), 3 (0.75 mmol), LiBr (1.0 mmol) and Pd catalyst (0.025 mmol) in 2 mL of solvent at 60 °C for 5 h.

^[b] GC yield, with naphthalene as the internal standard.

^[c] Isolated yield.

^[d] Determined by GC.

of Z:E isomers (entry 1, Table 1). This demonstrated that the vinylpalladium intermediate, generated by halopalladation of the C=C triple bond, could be successfully trapped by 2,3-butadienol under mild conditions. Encouraged by this result, we further examined the reaction conditions and the results are listed in Table 1.

Firstly, we studied the effect of leaving groups on the coupling reaction. Of the groups (X = OH, OBz,Br, OAc) we tested, 2,3-butadienyl acetate (3d) led to the best yield, albeit with moderate selectivity (entries 1-4, Table 1). Accordingly, 2,3-butadienyl acetate (3d) was chosen for screening of the solvent for this reaction (entries 5–9, Table 1). A promising result was obtained by the use of CH₃CN as the solvent, giving (Z)-4aa in 85% yield with an excellent Z-stereoselectivity (Z/E > 95/5 by GC). A brief survey of palladium sources proved $Pd(OAc)_2$ to be the best, while the use of other palladium sources, such as PdCl₂, PdBr₂, Pd(MeCN)₂Cl₂ and Pd(PhCN)₂Cl₂, led to no improveof the stereoselectivities (entries 10–13, ment Table 1). Thus, we chose $5 \mod \%$ of $Pd(OAc)_2$ as the catalyst, 2 equivalents of LiBr as halide sources, CH₃CN as the solvent, and 60°C as the optimized reaction conditions for the dienvlation reaction of haloalkynes.

With the optimal conditions in hand, we further investigated the scope and limits of this reaction. The reaction was found to be applicable to various bro-

	Table 2. Pd-catalyzed	dienylation of	haloalkynes	with 3d . ^[a]
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Entry	1	R/X	4	Yield [%] ^[b]	$Z/E^{[c]}$
1	1 a	Ph/Br	(Z)- 4 aa	85	>95/5
2	1b	<i>p</i> -Cl-C ₆ H ₄ /Br	(Z)-4ba	73	> 98/2
3	1c	Ph/Cl	(Z)-4ca	87	> 98/2
4	1d	p-F-C ₆ H ₄ /Cl	(Z)-4da	65	> 98/2
5	1e	p-Cl-C ₆ H ₄ /Cl	(Z)-4ea	81	> 98/2
6	1f	p-Br-C ₆ H ₄ /Cl	(Z)-4fa	78	> 98/2
7	1g	o-Br-C ₆ H ₄ /Cl	(Z)-4ga	77	>98/2
8	1ň	p-Me-C ₆ H ₄ /Cl	(Z)-4ha	71	> 98/2
9	1i	p-MeO-C ₆ H ₄ /Cl	(Z)-4ia	79	> 98/2
10	1j	m-MeO-C ₆ H ₄ /Cl	(Z)-4ja	80	>98/2
11	1ĸ	o-MeO-C ₆ H ₄ /Cl	(Z)-4ka	82	> 98/2
12	11	2-furan/Cl	(Z)-4la	58	>98/2
13	1m	2-thiophene/Cl	(Z)-4ma	67	> 98/2
14	1n	2-naphthalene/Cl	(Z)-4na	80	>98/2
15	10	$CH_3(CH_2)_4/Cl$	(Z)-40a	72	> 98/2
16	1p	TBSOCH ₂ CH ₂ /Cl	(Z)-4pa	67	> 98/2
17	1q	BnOCH ₂ /Cl	(Z)-4qa	82	> 98/2

^[a] Reaction conditions: 1 (0.5 mmol), 3d (0.75 mmol), LiBr (1.0 mmol) and Pd(OAc)₂ (0.025 mmol) in 2 mL of CH₃CN at 60 °C.

^[b] Isolated yield.

^[c] Determined by GC.

moalkynes and chloroalkynes, although the reaction of bromoalkynes was relatively sluggish. Both electron-rich and electron-deficient aromatic haloalkynes were smoothly converted into the dienylation products in good yields with excellent stereoselectivities (Table 2). For instance, the reaction of phenylethynyl chloride (1c) gave the dienvlation product (Z)-4ca in 87% yield with excellent stereoselectivity (Z/E > 98/2) (entry 3, Table 2). As for the sterically hindered chloroalkyne 1k, the reaction furnished the corresponding dienvlation product (Z)-4ka in a yield similar to that of (Z)-4ia or (Z)-4ja (entries 9–11, Table 2). Heteroaromatic chloroalkynes, such as 11 and 1m, provided the desired products (Z)-4la and (Z)-4ma in 58 and 67% yields, respectively (entries 12 and 13, Table 2). Moreover, aliphatic haloalkynes participated well in this reaction (entries 15–17, Table 2). For example, 1-chloroheptyne (10) reacted smoothly with 3d to afford the dienvlation product (Z)-40a in 72% yield. In sharp contrast, terminal alkynes, such as phenylacetylene, for instance, failed to react with **3d** to afford the desired product under the standard reaction conditions.

The regio- and stereochemistry of the dienylation products were established by NOE measurements and further confirmed by X-ray analysis. For instance, X-



Figure 1. X-ray structure of (Z)-4ca.

ray analysis^[8] of (Z)-**4ca** clearly indicated the structure (Figure 1).

The versatility of this protocol was further examined by the reaction of **1c** with a variety of functionalized 2,3-butadienyl acetates, and the results were summarized in Table 3.

As shown in Table 3, under the optimized reaction conditions, 4-substituted 2,3-butadienyl acetates, such

Table 3. Pd-catalyzed coupling of 1c with 3.^[a]



^[a] Reaction conditions: **1c** (0.5 mmol), **3** (0.75 mmol), LiBr (1.0 mmol) and Pd(OAc)₂ (0.025 mmol) in 2 mL of CH₃CN at 60 °C.

as **3e** and **3f**, afforded the desired dienylation products (1Z,3E)-**4ce** and (1Z,3E)-**4cf** in 69 and 65% yields, respectively (entries 1 and 2, Table 3). Remarkably, the (1Z,3E)-1,2-dihalo-3-vinyl-1,3-diene was detected as the single stereoisomer in both cases. It is believed that both the thermodynamic effect and the steric interaction between allene and vinlypalladium intermediate may account for the excellent stereoselectivity.^[9] However, further attempts to extend the reaction to 1-substituted or 2-subtituted 2,3-butadienyl acetates, such **3g** and **3h**, resulted in failure, majorly due to the unfavorable steric repulsion in the carbopalladation step (see proposed mechanism) (entries 3 and 4, Table 3).

Thus far, we have developed a highly efficient and stereoselective method for the synthesis of (1Z)-1,2-dihalo-3-vinyl-1,3-dienes. As we know, 1,3-dienes are valuable building blocks in organic synthesis, especially for the Diels-Alder reaction.^[10] Therefore, we examined the utility of (*Z*)-4ca in the cycloaddition reaction. To our delight, (*Z*)-4ca reacted smoothly with diethyl acetylenedicarboxylate (5) in toluene at reflux to generate the 1,4-cyclohexadiene derivative 6 in 76% yield. The subsequent dehydrogenation employing 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)^[11] led to the *cis*-1,2-dihalostyrene derivative 7 in 69% yield (Scheme 2).

Pioneered by Ma and others,^[12] it is widely documented that 1,3-dienes could be accessed by the carbopalladation of 2,3-allenyl alcohols or acetates. As such, a working mechanism as demonstrated in Scheme 3 was proposed for this Pd-catalyzed coupling



Scheme 2. Transformations of (*Z*)-4ca.



Scheme 3. Proposed mechanism for dienylation of alkynyl halides.

^[b] Isolated yield.

of haloalkynes with 2,3-butadienyl acetates. The haloalkyne **1** underwent the *trans*-addition^[13] pathway in the presence of excess halide to form the alkenyl-palladium intermediate **I**, followed by the carbopalladation reaction with 2,3-butadienyl acetate **3** to give an allyl-palladium intermediate **II**. Finally, a β -heteroatom elimination furnished the dienylation product (*Z*)-**4** and regenerated the palladium catalyst (Scheme 3).

To date, there is no precedent report of using allenes as electrophiles to trap intermediates resulting from halopalladation of acetylenes, probably due to the oligomerization of allenes in the presence of divalent palladium complexes.^[14] The success of this protocol, in our opinion, mainly originated from the observation that haloalkynes exhibit much more reactivity than terminal alkynes and allenes under the halopalladation reaction conditions (Scheme 1).

In summary, we have developed an efficient and practical procedure for the synthesis of (1Z)-1,2dihalo-3-vinyl-1,3-dienes with perfect control of stereochemistry through Pd-catalyzed dienylation of alkynyl halides using 2,3-butadienyl acetates. It embraces the halopalladation of acetylenes with the addition of allenes, and thus greatly broadens the scope and synthetic utility of the halopalladation reaction. In addition, the easy incorporation of the resultant polyene products into the Diels-Alder reaction makes it a rather interesting and efficient method for the synthesis of cyclic compounds. Further investigations on the synthetic applications of this protocol are currently underway in this group.

Experimental Section

General Procedure for Pd-Catalyzed Coupling of Alkynyl Halides with 2,3-Butadienyl Acetates

To a mixture of **3d** (84 mg, 0.75 mmol) and Pd(OAc)₂ (5.6 mg, 0.025 mmol) in 2 mL of acetonitrile was added **1a** (73 mg, 0.5 mmol). After stirring for 5 h at 60 °C, the reaction mixture was concentrated and purified by column chromatography on silica (petroleum ether) to give (*Z*)-**4aa** as a yellow solid; yield: 115 mg (85%); mp 59–61 °C (petroleum ether); *Z/E*:> 95/5. The stereochemistry was assigned by NOE measurements. ¹H NMR (CDCl₃, 400 MHz): δ =5.11 (s, 2H), 5.32 (d, *J*=10.8 Hz, 1H), 5.47 (d, *J*=17.6 Hz, 1H), 6.21 (dd, *J*=17.6, 10.8 Hz, 1H), 7.26–7.28 (m, 3H), 7.33–7.35 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ =118.1, 121.4, 122.7, 126.7, 128.0 (2C), 128.3 (2C), 128.7, 135.3, 139.3, 145.9; MS (70 eV, EI): *m/z* (%)=316 (2.5), 314 (4.6), 312 (M⁺, 2.5), 235 (22), 233 (M⁺-Br, 21); HR-MS: *m/z*= 311.9154, calcd. for C₁₂H₁₀Br₂: 311.9149.

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- [8] Crystallographic data for (*Z*)-4ca: $C_{12}H_{10}BrCl$ (267.97), monoclinic, space group *P*21/c, *a*=7.224(15) Å, *b*= 9.676(2) Å, *c*=16.487(4) Å, *U*=1135.1(4) Å³, *Z*=4, specimen 0.298×0.141×0.088 mm³, *T*=296(2) K, Siemens P4 diffractometer, absorption coefficient 3.814 mm⁻¹, reflections collected 6924, independent reflections 1996 [*R*(int)=0.0467], refinement by fullmatrix least-squares on *F*², data/restraints/parameters

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1996/0/127, goodness-of-fit on $F^2 = 1.037$, final *R* indices $[I > 2 \sigma(I)]$ R1 = 0.0445, wR2 = 0.1048, *R* indices (all data) R1 = 0.0692, wR2 = 0.1118, largest diff. peak and hole 0.793 and -0.485 eÅ⁻³. Crystallographic data for the structure (*Z*)-**4ca** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 809448. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[9] The steric interactions between vinlypalladium intermediates and 2,3-butadienyl acetates were suggested as follows:

$$(1Z,3E)-4 \leftarrow \begin{bmatrix} Br & CI \\ Ph & Pd \\ H & C & OAc \end{bmatrix} vs. \begin{bmatrix} Br & CI \\ Ph & Pd \\ R & C & OAc \end{bmatrix} \cdots (1Z,3Z)-4$$

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