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Palladium-catalyzed highly regio- and stereoselective synthesis of (1*E*)- or (1*Z*)-1,2-dihalo-1,4-dienes *via* haloallylation of alkynyl halides†

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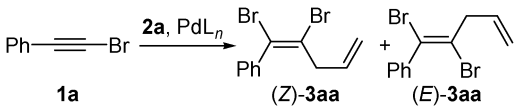
A highly efficient and selective synthesis of (1*E*)- or (1*Z*)-1,2-dihalo-1,4-dienes *via* Pd-catalyzed coupling of haloalkynes and allylic halides is described. The (1*E*)-1,2-dihalo-1,4-dienes were generated in good yields with excellent stereoselectivities (1*E*/1*Z* up to > 98/2), while (1*Z*)-1,2-dihalo-1,4-dienes were produced in excellent yields and stereoselectivities (1*Z*/1*E* up to > 98/2) by simply adding stoichiometric lithium halides.

Transition-metal-catalyzed carbon–carbon or carbon–heteroatom bond formation is a central theme in organic synthesis.[1] In particular, the halopalladation reaction of acetylenes has attracted dramatic interests in the past decades, since it has proven to be a powerful method for the highly efficient and atom-economic formation of carbon–carbon and carbon–halide bonds in a single step.[2] Despite the great success achieved along the line with halopalladation of electronic- or steric-unbalanced acetylenes, such as terminal alkynes,[3] the alkynes containing electron-withdrawing[3a–f] or coordination groups,[4,5] the halopalladation of unsymmetrical internal alkynes remains to be challenging. In our efforts to develop new reactions involving the halopalladation process,[6] we report herein the first palladium-catalyzed haloallylation[7] reaction of alkynyl halides, in which regio- and stereodefined 1,2-dihalo-1,4-dienes were efficiently synthesized.

To explore the haloallylation reaction of haloalkynes, phenylethynyl bromide (**1a**) and allyl bromide (**2a**) were chosen for the initial screening. In the presence of 5 mol% of $Pd(OAc)_2$ as a catalyst, the starting materials were completely consumed within 30 min at room temperature in THF, providing **3aa** in 76% yield with a high *E*-stereoselectivity (*E*/*Z* = 98/2 by GC). Encouraged by this result, we looked further into the reaction conditions and the results are summarized in Table 1.

We first checked the solvents for this reaction. Polar solvents such as acetonitrile and *N*,*N*-dimethylformamide (DMF) favored the formation of the *Z*-isomer (entries 2 and 3, Table 1), whereas non-coordinating solvents, such as toluene and CH_2Cl_2, significantly increased the yields and stereoselectivities (entries 4 and 5, Table 1). CH_2Cl_2 was then chosen as the solvent and other palladium reagents, such as $PdBr_2$ and $PdCl_2$, were tested as the catalyst, unfortunately, the products were produced in lower yields (entries 5 and 6, Table 1). Therefore, we selected 5 mol% of $Pd(OAc)_2$ as the catalyst and CH_2Cl_2 as the solvent as the optimized condition A for the *cis*-haloallylation reaction of haloalkynes.

Table 1 Optimization of the reaction conditions for the haloallylation of phenylethynyl bromide[a]



1a (*Z*)-**3aa** (*E*)-**3aa**

Entry	PdX_2	Solvent	LiBr/equiv.	Yield[b] (%)	*E*/*Z*[c]
1	$Pd(OAc)_2$	THF	/	76	98/2
2	$Pd(OAc)_2$	DMF	/	70	23/77
3	$Pd(OAc)_2$	MeCN	/	60	42/58
4	$Pd(OAc)_2$	Toluene	/	84	> 98/2
5	$Pd(OAc)_2$	CH_2Cl_2	/	85	> 98/2
6	$PdCl_2$	CH_2Cl_2	/	79	> 98/2
7	$PdBr_2$	CH_2Cl_2	/	82	> 98/2
8	$Pd(OAc)_2$	CH_2Cl_2	1.0	86	97/3
9	$Pd(OAc)_2$	DMF	1.0	60	16/84
10	$Pd(OAc)_2$	HOAc	1.0	73	5/95
11	$Pd(OAc)_2$	HOAc	2.0	80	< 3/97
12	$Pd(OAc)_2$	HOAc	5.0	74	< 2/98

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol) and Pd catalyst (0.025 mmol) in 2 mL of solvent at 23 °C. [b] Isolated yields. [c] Determined by GC.

While now we have the condition A for the efficient and selective synthesis of (*E*)-**3aa**, we wish to obtain (*Z*)-**3aa** through introducing additional halide sources, since it is known that the halopalladation reaction may undergo *trans*-addition in the presence of halides, in sharp contrast to the well-documented *cis*-insertion in the absence or at low concentrations of halides.[8] As such, the reactions were performed in the presence of halides, and as expected, the addition of 1.0 equiv. of LiBr increased the selectivity of the (*Z*)-isomer from 77% to 84% in DMF (entries 2 *vs.* 9, Table 1). The use of HOAc as the solvent further raised the selectivity of (*Z*)-**3aa** to 95% (entry 10, Table 1). Increasing the amount of LiBr did improve the selectivity; however, a relatively lower yield was observed using 5.0 equiv. of LiBr as an additive, due to the generation of the homocoupling product of **1a** (entries 11 and 12, Table 1). The stereochemistry of the haloallylation

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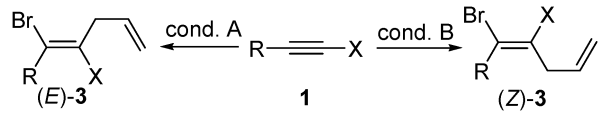
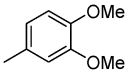
Table 2 Pd-catalyzed haloallylation of haloalkynes with **2a**[a]



Entry	1	R	X	Cond.	3	Yield[b] (%)	E/Z[c]
1	**1a**	Ph	Br	A	(*E*)-**3aa**	85	>98/2
2	**1a**	Ph	Br	B	(*Z*)-**3aa**	80	<3/97
3	**1b**	Ph	Cl	A	(*E*)-**3ba**	83	>98/2
4	**1b**	Ph	Cl	B	(*Z*)-**3ba**	81	<2/98
5	**1c**	$TBSO(CH_2)_2$	Br	A	(*E*)-**3ca**	65	>98/2
6	**1c**	$TBSO(CH_2)_2$	Br	B	(*Z*)-**3ca**	62	<2/98
7	**1d**	$TBSO(CH_2)_2$	Cl	A	(*E*)-**3da**	84	>98/2
8[c]	**1d**	$TBSO(CH_2)_2$	Cl	B	(*Z*)-**3da**	68	<2/98
9	**1e**	CH_2OAc	Br	A	(*E*)-**3ea**	62	>98/2
10	**1f**	C_9H_{19}	Br	A	(*E*)-**3fa**	86	>98/2
11	**1g**	1-Cyclohexenyl	Br	A	(*E*)-**3ga**	66	>98/2
12	**1h**	*p*-OMe–C_6H_4	Br	A	(*E*)-**3ha**	78	>98/2
13	**1i**	*p*-Cl–C_6H_4	Br	A	(*E*)-**3ia**	76	>98/2
14	**1j**		Br	A	(*E*)-**3ja**	91	>98/2

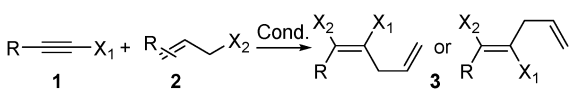
[a] Cond. A = **1** (0.5 mmol), **2a** (0.75 mmol) and $Pd(OAc)_2$ (0.025 mmol) in 2 mL of CH_2Cl_2 at 23 °C; cond. B = **1** (0.5 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol) and LiBr (1.0 mmol) in 2 mL of HOAc at 23 °C. [b] Isolated yields. [c] Determined by GC.

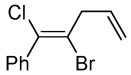
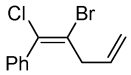
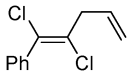
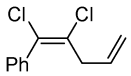
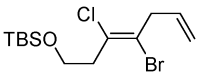
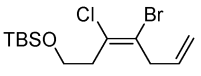
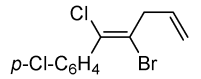
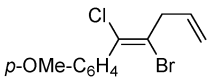
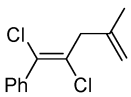
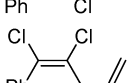
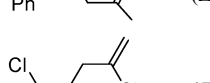
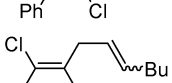
products (*E*)-**3aa** and (*Z*)-**3aa** was established by NOE measurements and consistent with the related literature report.[9] Thus, for the *trans*-haloallylation products, we chose 5 mol% of $Pd(OAc)_2$ as the catalyst, 2.0 equiv. of lithium halides as the additives and HOAc as the solvent for the standard condition B.

With the optimized reaction conditions A and B in hand, we next turned our attention to the scope of the haloallylation reaction. As shown in Table 2, both bromoalkynes and chloroalkynes are good coupling partners for this Pd-catalyzed bromoallylation transformation. For example, phenylethynyl chloride (**1b**) reacted with **2a** in the same fashion as **1a**, and afforded the *cis*-allylation product (*E*)-**3ba** in 83% yield with excellent stereoselectivity (E/Z > 98/2) under the optimized condition A, or furnished the *trans*-allylation adduct (*Z*)-**3ba** in 81% yield and with Z/E > 98/2 selectivity if the optimized condition B was employed (entries 3 and 4, Table 2). The conventional protecting groups, such as *tert*-butyldimethylsilyl (TBS) and acetyl (Ac), could be well tolerated under the reaction conditions (entries 5–9, Table 2). Aliphatic haloalkynes also participated well in this reaction. Both the primary and secondary alkyl substituted bromoalkynes **1f** and **1g** could undergo the same reaction to give (*E*)-**3fa** and (*E*)-**3ga** in 86 and 66% yields, respectively (entries 10 and 11, Table 2). We also examined the electronic effects on the aromatic rings and found that both electron-rich and electron-deficient aromatic haloalkynes were smoothly converted into the desired products in good yields and excellent stereoselectivities (entries 12–14, Table 2).

The versatility of this protocol was further demonstrated by the reactions of various allylic halides (Table 3). Allyl chloride (**2b**) reacted smoothly with numerous alkynyl halides to give the corresponding 1,2-dihalo-1,4-diene products in good yields (entries 1–8, Table 3). While 2-methyl-substituted allyl chloride (**2c**) afforded the desired (*E*)-**3bc** and (*Z*)-**3bc** in 83 and 72% yields, respectively (entries 9 and 10, Table 3), interestingly,

Table 3 Pd-catalyzed haloallylation of haloalkynes with various allylic chlorides[a]

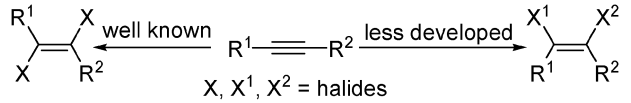


Entry	1	2	Cond.	Product		Yield/%[b]
1	**1a**	**2b**	A		(*E*)-**3ab**	85 (>98/2)[c]
2	**1a**	**2b**	B		(*Z*)-**3ab**	80 (11/89)[c]
3	**1b**	**2b**	A		(*E*)-**3bb**	89 (>98/2)[c]
4	**1b**	**2b**	B		(*Z*)-**3bb**	83 (<2/98)[c]
5	**1c**	**2b**	A		(*E*)-**3cb**	81 (>98/2)[c]
6	**1c**	**2b**	B		(*Z*)-**3cb**	72 (<2/98)[c]
7	**1i**	**2b**	A		(*E*)-**3ib**	90 (>98/2)[c]
8	**1f**	**2b**	A		(*E*)-**3fb**	81 (>98/2)[c]
9	**1f**	**2c**	A		(*E*)-**3bc**	83 (>98/2)[c]
10	**1b**	**2c**	B		(*Z*)-**3bc**	72 (<2/98)[c]
11	**1b**	**2d**	A		(*E*)-**3bd**	39 (>98/2)[c]
12	**1a**	**2e**	A		**3ae**	67 (50/50)[d]

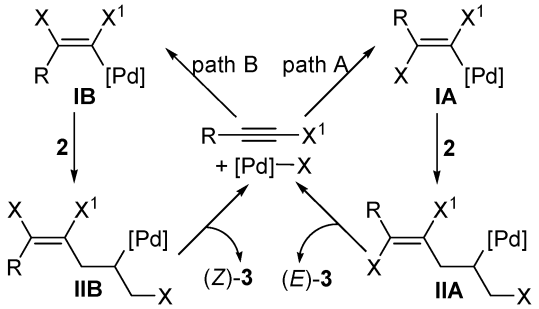
[a] Cond. A = **1** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol) and **2** (0.75 mmol) in 2 mL of CH_2Cl_2 at 23 °C; cond. B = **1** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), **2** (0.75 mmol) and LiBr or LiCl (1.0 mmol) in 2 mL of HOAc at 23 °C. [b] Isolated yields. [c] The ratio of 1*E*/1*Z*. [d] The ratio of 4*E*/4*Z*.

2-chloro-substituted allyl chloride (**2d**) afforded (*E*)-**3bd** in only 39% yield (entry 11, Table 3). The sharp contrast suggested great electronic effect on the electrophiles: the more electron-rich allyl halides are, the better reactivity they exhibited towards the halopalladation reaction. As for the secondary allylic chloride, 3-chloro-1-heptene (**2e**), for example, provided the bromoallylation product **3ae** in 67% yield with 50 : 50 mixture of Z : E isomers (entry 12, Table 3). Allyl halides having an internal C–C double bond, such as crotyl bromide **2f** and cinnamyl bromide **2g**, failed to give the desired products.

Therefore, we have been able to develop a rather practical, efficient, and most importantly, highly versatile method for the



Scheme 1 Two possible pathways for 1,2-dihaloalkenes.



Scheme 2 Proposed mechanism for the haloallylation of alkynyl halides.

synthesis of 1,2-dihalogenated (*E*)- or (*Z*)-1,4-dienes, depending on the condition A or B employed. Even though 1,2-dihaloalkenes are valuable synthetic building blocks in organic synthesis, there are not too many methods available for their synthesis. Considering the relatively easy preparation of *trans*-1,2-dihaloalkenes from the electrophilic halogenation of alkynes,[10] there are rather limited examples for the synthesis of *cis*-1,2-dihaloalkenes,[11] especially the differentially halogenated ones (Scheme 1). However, with the optimized conditions A and B presented here, we can easily synthesize both *trans*- and *cis*-1,2-dihalo-1,4-dienes in a highly regio- and stereoselective fashion. In addition, the resulting 1,2-dihalo-1,4-dienes could serve as useful intermediates for the rapid synthesis of stereodefined tetrasubstituted alkenes,[12] which represent another challenging targets in organic synthesis. Further development of our methods towards the synthesis of these targets is on the way.

The possible mechanism for this Pd-catalyzed haloallylation of alkynyl halides is proposed in Scheme 2. The dichotomy of this process originates from the observation that halopalladation can undergo a *cis*- or *trans*-pathway under different reaction conditions.

In the absence of halides, haloalkyne **1** reacted with the Pd–X bond in a *cis*-insertion pathway to give an alkenyl palladium intermediate **IA**. The excellent regioselectivity in this step may come from the relatively small steric hindrance of the halogen atom compared with the carbon chain or aromatic ring.[13] Then, **IA** underwent carbopalladation with allylic halides to afford alkyl palladium intermediate **IIA**, followed by the β-heteroatom elimination to furnish the *cis*-haloallylation product (*E*)-**3** and to regenerate the palladium catalyst (path A, Scheme 2).

On the other hand, the present excess halides could undergo S_N2-like reaction to attack Pd(II)-activated alkynyl halides in polar solvents and resulted in the *trans*-halopalladation adduct **IB**. Then, the same carbopalladation-β-heteroatom elimination sequence gave the *trans*-haloallylation product (*Z*)-**3** (path B, Scheme 2).

In summary, we have developed an efficient and practical procedure for the synthesis of (1*E*)- or (1*Z*)-1,2-dihalo-1,4-dienes with palladium-catalyzed haloallylation of alkynyl halides as the key step. This procedure is a significant advance in the halopalladation reaction because it represents the first regio- and stereoselective halopalladation process of the electron-rich internal alkynes. Further investigation of the reaction mechanism, as well as the synthetic applications of this protocol for the establishment of tetrasubstituted alkenes are currently in progress.

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