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Synthesis of *cis*-1,2-Dihaloalkenes Featuring Palladium-Catalyzed Coupling of Haloalkynes and α,β-Unsaturated Carbonyls

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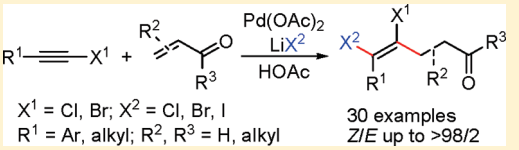
Supporting Information

ABSTRACT: A highly regio- and stereoselective method for the synthesis of *cis*-1,2-dihaloalkenes through Pd-catalyzed coupling of haloalkynes and α,β-unsaturated carbonyls has been reported. Excellent stereoselectivities (*Z*/*E* up to >98:2) were observed in most cases. This method was subsequently applied to synthesize the functionalized conjugated enyne via the mono-Sonogashira coupling reaction of *cis*-1-chloro-2-iodoalkene.



Halogenated organic compounds are naturally occurring in living organisms, and they have also been frequently used as important building blocks in multistep synthesis, material science, and the chemical industry.[1] In particular, 1,2-dihaloalkenes have attracted considerable attention in the past decades, mainly due to the coupling reactions of the two adjacent carbon−halide bonds with various nucleophiles for the rapid formation of stereodefined tri- or tetrasubstituted alkenes.[2]

The synthesis of *trans*-1,2-dihaloalkenes is accomplished normally by the electrophilic halogenation of alkynes (eq 1, Scheme 1).[3] For example, Ogilvie et al. described a highly selective iodochlorination reaction of alkynes employing tetrabutylammonium iodide and dichloroethane,[3c,d] in which *trans*-1-chloro-2-iodoalkene was obtained as the single isomer. Despite the great prevalence of preparing *trans*-1,2-dihaloalkenes in the literature, interestingly, there are rather limited methods for the effective synthesis of stereoselectively pure *cis*-1,2-dihaloalkene derivatives (eq 2, Scheme 1).[4] A promising report for the stereoselective synthesis of *cis*-1,2-dihaloalkenes came from Whiting's group, where the iodochlorination of alkynes occurred with iodine monochloride and tetraethylammonium iodide.[5] However, this method is not stereoselective yet in some cases.

Apart from the selectivity issue, the conventional electrophilic halogenation reactions involve hazardous, toxic, and corrosive electrophilic halogen sources, which further limits their applications in organic synthesis. As such, it is highly desirable to develop an environmentally benign and selective method for the preparation of *cis*-1,2-dihaloalkenes from the readily available starting materials. Herein, we report a highly regio- and stereoselective protocol for the synthesis of *cis*-1,2-dihaloalkenes featuring the Pd-catalyzed haloalkynes−α,β-unsaturated carbonyls coupling reaction.[6]

To test the feasibility, phenylethynyl bromide (**1a**) and acrolein (**2a**) were chosen for the initial screening. In the presence of 5 mol % of $PdCl_2$ and 1.0 equiv of LiBr (**3a**) as an additive, **1a** was completely consumed within 1 h at room temperature in HOAc, providing **4** in 75% yield with a high *Z*-stereoselectivity (*Z*/*E* = 90:10). Inspired by this promising result, we further examined the reaction conditions and the results were summarized in Table 1.

As shown in Table 1, among all the palladium sources we examined, $Pd(OAc)_2$ proved to be the best, affording product **4** in 91% GC yield and with excellent stereoselectivity (*Z*/*E* > 98:2) (entries 1−4, Table 1). The stereochemistry of the product was determined by NOE measurements and further confirmed by its conversion into the literature-known (*Z*)-1,2-dibromo-1-phenylpropene.[7] Increasing the amount of LiBr only slightly improved the yields, for example, the use of 2.0 and 5.0 equiv of LiBr gave **4** in 91% and 92% yields, respectively (entries 5 and 6, Table 1). The replacement of LiBr by other bromide sources, such as KBr and NaBr, resulted in lower yields (entries 7 and 8, Table 1). We also screened the solvents for the reaction, and of all the solvents we tested, HOAc turned out to be the best (entries 8−10, Table 1).

Therefore, the optimal reaction conditions consisted of 5 mol % of $Pd(OAc)_2$ as the catalyst, 2.0 equiv of lithium halides as halide sources, and HOAc as the solvent. As demonstrated in Table 2, the reaction could be scaled up to 10 mmol to give product **4** in 80% yield (entry 1, Table 2). Then, we turned our attention to the stereoselective synthesis of various *cis*-1,2-dihaloalkenes using our protocol, and the scope and limits of this reaction were illustrated in Table 2. Various aryl and alkyl ethynyl bromides could react with **2** to give the desired *cis*-1,2-dibromoalkene products in good to excellent yields, and particularly noteworthy was that excellent stereoselectivity (*Z*/*E* > 98:2) was observed (entries 1−3, Table 2).

Due to the readily easy elimination process[2d] of *cis*-1,2-dibromoalkenes occurring in Pd-catalyzed cross-coupling reactions,[8] we set up to prepare *cis*-1-chloro-2-haloalkenes, in recognition of the chemically more stable feature of the C−Cl bond than the C−Br bond. In addition, the well-established differentiated reactivity of C−Cl and C−Br or C−I bonds may provide us a better chance to install different groups in a regioselective

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Scheme 1. Two Possible Pathways for 1,2-Dihaloalkenes

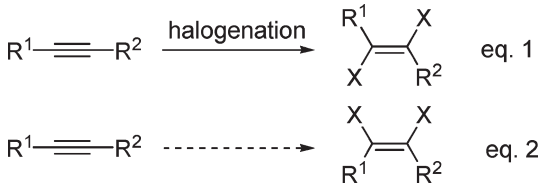
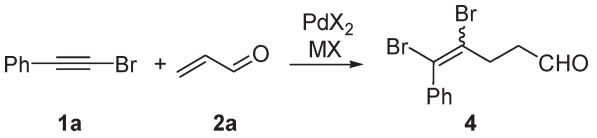


Table 1. Selected Results of Screening the Reaction Conditions[a]



entry	PdX_2	solvent	MX (equiv)	yield (%)[b,c]	Z/E[d]
1	$PdCl_2$	HOAc	LiBr (1.0)	75	90:10
2	$PdBr_2$	HOAc	LiBr (1.0)	79	>98:2
3	$Pd(CF_3CO_2)_2$	HOAc	LiBr (1.0)	75	96:4
4	$Pd(OAc)_2$	HOAc	LiBr (1.0)	85	>98:2
5	$Pd(OAc)_2$	HOAc	LiBr (2.0)	91 (82[c])	>98:2
6	$Pd(OAc)_2$	HOAc	LiBr (5.0)	92	>98:2
7	$Pd(OAc)_2$	HOAc	NaBr (2.0)	84	>98:2
8	$Pd(OAc)_2$	HOAc	KBr (2.0)	42	>98:2
9	$Pd(OAc)_2$	HCOOH	LiBr (2.0)	52	>98:2
10	$Pd(OAc)_2$	1 N HCl	LiBr (2.0)	6	>98:2

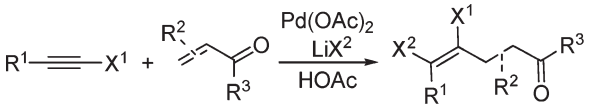
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), MX and Pd catalyst (0.025 mmol) in 2.5 mL of solvent at 23 °C. [b] GC yields, with naphthalene as the internal standard. [c] Isolated yield. [d] Determined by GC.

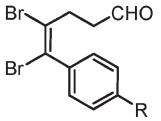
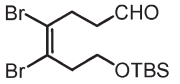
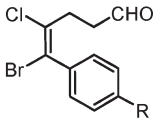
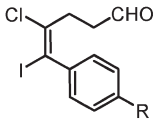
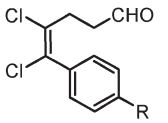
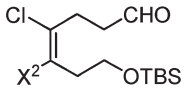
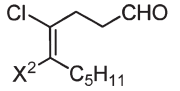
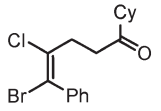
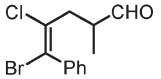
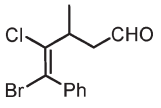
fashion. Thus, we focused on chloroalkynes as the substrates to synthesize all kinds of 1,2-dihaloalkenes, with the emphasis on the differentially halogenated ones.

As expected, different types of *cis*-1-bromo-2-chloroalkenes bearing either electron-deficient or electron-rich groups were successfully generated in good yields and with excellent stereoselectivities under the optimal reaction conditions (entries 4−9, Table 2). Furthermore, *cis*-1-chloro-2-iodoalkenes were prepared with excellent stereoselectivities in the presence of LiI (**3b**), albeit in moderate yields and at elevated temperature (80 °C) (entries 10−15, Table 2). Lithium chloride (**3c**) was also smoothly incorporated into the reaction and afforded the desired *cis*-1,2-dichloroalkenes in good yields and excellent stereoselectivities (Z/E > 98:2), except that 1,2-dichloroalkene products **23** and **24** were obtained with 94:6 and 67:33 mixture of Z/E isomers, respectively (entries 20 and 21, Table 2).

Aliphatic haloalkynes also participated well in this reaction, and resulted in the *cis*-1-bromo-2-chloro-, *cis*-1-chloro-2-iodo-, and *cis*-1,2-dichloroalkenes in a highly stereoselective fashion and with good yields. For instance, the *cis*-1-bromo-2-chloroalkene **25** was generated in 81% yield and with excellent stereoselectivity (Z/E > 98:2) in the presence of LiBr, whereas *cis*-1,2-dichloroalkene **27** was obtained as a single *Z*-isomer in 77% yield with LiCl as the halide source (entries 22−24, Table 2).

Table 2. Scope and Limits of the Reaction[a]



entry	X^2	R	product		yield (%)[b]	Z/E[c]
1	Br	H		**4**	82 (80)[d]	>98:2
2	Br	Cl		**5**	71	>98:2
3	Br	/		**6**	72	>98:2
4	Br	F		**7**	70	>98:2
5	Br	Cl		**8**	73	>98:2
6	Br	Br		**9**	78	>98:2
7	Br	H		**10**	87	>98:2
8	Br	Me		**11**	72	>98:2
9	Br	OMe		**12**	71	>98:2
10	I	F		**13**	49	>98:2
11	I	Cl		**14**	56	>98:2
12	I	Br		**15**	55	>98:2
13	I	H		**16**	65	>98:2
14	I	Me		**17**	53	93:7
15	I	OMe		**18**	52	>98:2
16	Cl	F		**19**	78	>98:2
17	Cl	Cl		**20**	86	>98:2
18	Cl	Br		**21**	76	>98:2
19	Cl	H		**22**	76	>98:2
20	Cl	Me		**23**	80	94:6
21	Cl	OMe		**24**	75	67:33
22	Br	/		**25**	81	>98:2
23	I	/		**26**	65	>98:2
24	Cl	/		**27**	77	>98:2
25	Br	/		**28**	78	>98:2
26	I	/		**29**	54	>98:2
27	Cl	/		**30**	81	>98:2
28	Br	/		**31**	67	>98:2
29	Br	/		**32**	42	>98:2
30	Br	/		**33**	50	>98:2

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75−2.5 mmol), LiX^2 (1.0 mmol), and $Pd(OAc)_2$ (0.025 mmol) in 2.5 mL of HOAc at 23 °C (80 °C for LiI). [b] Isolated yields. [c] Determined by GC. [d] Isolated yield on 10 mmol scale.

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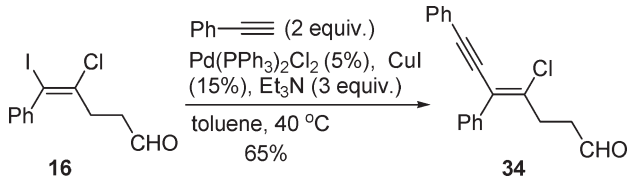
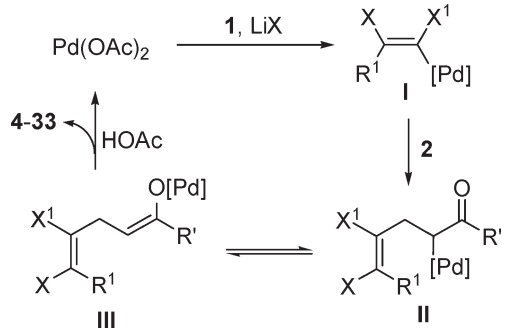
Scheme 2. The Mono-Sonogashira Coupling of 16



Scheme 3. Proposed Mechanism for Pd-Catalyzed Coupling of Haloalkynes and α,β-Unsaturated Carbonyls



Finally, we checked other α,β-unsaturated carbonyls as the electrophiles for this reaction. For example, the reaction of 1-cyclohexyl-2-propenone (**2b**) afforded *cis*-1-bromo-2-chloroalkene **31** in 67% yield and excellent setereoselectivity (Z/E > 98:2), while substituted α,β-unsaturated carbonyls, such as 2-methylacrolein (**2c**) and crotonaldehyde (**2d**), only led to **32** and **33** in 42% and 50% yields, respectively (entries 28−30, Table 2). The sharp contrast suggested distinctive steric effect on the electrophiles.

As such, we have developed a rather practical and versatile method for the synthesis of *cis*-1,2-dihaloalkene derivatives. As we mentioned above, 1,2-dihaloalkenes could serve as useful intermediates for the rapid synthesis of highly functionalized alkenes. Thus, we made some primary efforts along this line. For instance, treatment of *cis*-1-chloro-2-iodoalkene **16** with 2 equiv of phenylacetylene in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 15 mol % of CuI in toluene at 40 °C gave the conjugated enyne **34** in 65% yield, and the untouched C−Cl bond of **34** may be further utilized for late-stage modification in organic synthesis. In sharp contrast, the reaction of *cis*-1,2-dibromoalkene product **4** failed to give the desired product under the Sonogashira coupling[9] conditions (Scheme 2).

The possible mechanism for this Pd-catalyzed coupling of alkynyl halides with α,β-unsaturated carbonyls is proposed in Scheme 3. Pioneered by Kaneda[10a] and Lu,[11a−c] the halopalladation reaction[10,11] has had great success in the past decades. It is widely accepted that the halopalladation reaction may undergo *trans*-addition in the presence of excess halide sources.[12] As such, the haloalkyne **1** underwent the *trans*-addition pathway in the presence of an excess of halides to form the *trans*-halopalladation adduct **I**, followed by the carbopalladation reaction with α,β-unsaturated carbonyls to afford an alkyl palladium intermediate **II** or the enolate intermediate **III**. Finally, the protonolysis of the O−Pd or C−Pd bonds furnished the *cis*-dihaloalkene products and regenerated the palladium catalyst (Scheme 3).

In summary, we have developed a facile and practical method for the synthesis of *cis*-1,2-dihaloalkenes with excellent stereoselectivities via the palladium-catalyzed coupling of alkynyl halides and α,β-unsaturated carbonyls under mild reaction conditions. It represents a highly regio- and stereoselective halopalladation process of haloalkynes. Further investigations of the synthetic applications of this reaction for the establishment of tri- or tetrasubstituted alkenes are currently underway in this group.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *cis*-1,2-Dihaloalkenes. To a solution of LiBr (87.0 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and **2a** (0.11 mL, 2.5 mmol) in 2.5 mL of HOAc was added **1a** (91.0 mg, 0.5 mmol). After the reaction mixture was stirred at room temperature for 1 h, it was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica to give 130.1 mg (yield: 82%) of **4** as a colorless oil: Z/E > 98:2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (s, 4H), 7.28−7.37 (m, 5H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 42.8, 123.9, 127.8, 128.3 (2C), 128.7 (2C), 129.0, 138.9, 199.7; IR (neat, cm^{-1}) 3049, 2923, 1724, 1622; MS (EI, m/z) 320 (1), 318 (2), 316 (M^+, 1), 239 (100), 237 ($M^+ - {}^{79}$Br, 88); HRMS (ESI) calcd for $C_{11}H_{10}Br_2O$ 315.9089, found 315.9097.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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