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Palladium-Catalyzed Stereoselective Hydrogenolysis of Conjugated 1,1-Dibromo-1-alkenes to (*Z*)-1-Bromo-1-alkenes. An Application to Stepwise and One-Pot Synthesis of Enediynes and Dienynes

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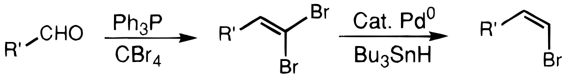
Palladium-catalyzed coupling reactions of alkenyl halides with alkenyl or alkynyl metals have been used widely in organic synthesis.[1] For this reason, alkenyl halides have become increasingly important. Particularly, geometrically pure alkenyl halides have been required in the stereospecific preparation of conjugated polyenes and enynes.[2] A number of important natural products possess a *(Z)-olefin* unit in conjugated structures (e.g., rhodopsins,[3] eicosanoids,[4] and enediyne antibiotics[5]), all of which exhibit significant biological activities. For the synthesis of such a unique structural moiety, geometrically pure (*Z*)-1-halo dienes or (*Z*)-1-halo enynes (Figure 1) are essential. In fact, some (*Z*)-(chloroethenyl)-acetylenes have been employed for the preparation of enediynes.[6] Several methods were reported on stereoselective preparation of (*Z*)-1-halo alkenes.[7] However, they could not be used in conjugated systems.[8] Herein, we disclose a new and reliable procedure for preparing geometrically pure (*Z*)-1-bromo dienes and (*Z*)-1-bromo enynes based on Pd-catalyzed hydrogenolysis of 1,1-dibromo dienes or 1,1-dibromo enynes with Bu$_3$SnH. These are then used for either stepwise or one-pot construction of dienynes and enediynes by the Sonogashira−Castro reaction.[9]

The typical reaction sequence is described in Scheme 1. First 1,1-dibromo-1-alkenes were prepared by C-1 homologation of the aldehydes by the standard procedure.[10] The stereoselective hydrogenolysis was carried out in benzene with a slight excess of Bu$_3$SnH in the presence of Pd(PPh$_3$)$_4$ (4 mol %).[11] Results of the bromo dienes, trienes, and enynes syntheses are listed in Table 1.

Figure 1.

Scheme 1



R' = Alkenyl or Alkynyl

The hydrogenolysis proceeded very cleanly with high stereoselectivity to give the geometrically pure (*Z*)-bromoalkenes in good yields.[12] The reactions were mostly complete within 1 h at room temperature, and rate enhancement was observed in the conjugated systems.[13] For example, the reaction of 1,1-dibromo triene **1b** was approximately 4 times faster than that of 1,1-dibromo diene **1a**, while conjugation with a phenyl ring also accelerated the reaction (compare entries 5 and 6). When the reactions of (*E*)- and (*Z*)-1,1-dibromo 1,3-dienes **1c** and **1d** were examined under the above reaction conditions, the conjugated alkenyl moiety retained its stereochemistry completely. 1,1-Dibromoalkenes **1e** and **1f**, conjugated with an alkynyl group, gave (*Z*)-bromo enynes **2e** and **2f** in 69 and 63% yields. It was confirmed that a hydride source for the hydrogenolysis was provided from Bu$_3$SnH by the fact that the use of Bu$_3$SnD afforded the deuterogenolysis product fully incorporated with deuterium at the terminal olefinic position.[14]

The palladium catalyst was essential for the reactions and the selectivity.[15] The reaction was complete when an approximately equal molar amount of the Bu$_3$SnH was consumed. On the other hand, when a large excess of Bu$_3$SnH was employed, over hydrogenolysis took place leading to terminal alkenes. The differentiation of the *gem*-dibromide is quite interesting,[16] because the at-

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(6) (a) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, S. V.; Dai, W.-M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890. (b) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harlin, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.

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(8) Although some (*Z*)-1-halo-1,3-dienes have been prepared, the geometrical purities were not satisfactory. (a) Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989**, *30*, 5261. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.

(9) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(10) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745. The conjugated 1,1-dibromoalkenes were obtained in 60−95% yields.

(11) A typical procedure consists of the following: To a mixture of 1,1-dibromoalkene (1 mmol) and Pd(PPh$_3$)$_4$ (4 mol %) in benzene (9 mL) was added Bu$_3$SnH (1.05−1.1 mmol) in benzene (3 mL), and the mixture was stirrred for 15−60 min at room temperature. Although (*Z*)-1-bromoalkene was isolated at this stage, the successive coupling reaction with alkyne was carried out. To the reaction mixture were added alkyne (1.5 mmol), CuI (30 mol %), and diisopropylamine (6 mmol), and the reaction was conducted at room temperature for 15−60 min.

(12) The (*E*)-isomer could not be detected by NMR in the crude mixture. The Pd-catalyzed hydrogenolysis of simple 1-iodo-1-alkenes was reported by Utimoto et al. Although it was highly stereospecific, the reaction of 1-bromo-1-alkenes was reported to be sluggish (see: Taniguchi, M.; Takeyama, Y.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2593).

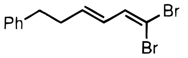
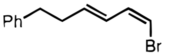
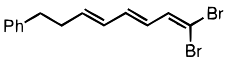
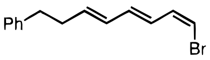
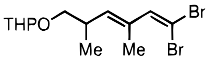
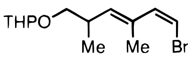
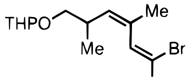
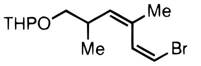
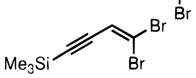
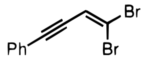
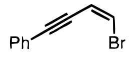
(13) The hydrogenolysis of simple 1,1-dibromo-1-alkenes also worked well.

(14) Other reducing reagents such as triethylsilane, tris(trimethylsilyl)silane, and formic acid were ineffective.

(15) In the absence of the palladium catalyst, the reaction was very slow and the yield was very poor. The hydrogenolysis under the radical conditions (e.g., catalytic Et$_3$B and Bu$_3$SnH) gave complex mixtures including (*E*)- and (*Z*)-isomers.

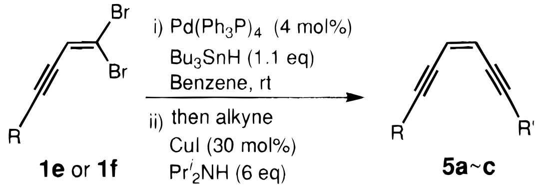
(16) For differentiation of the two bromo groups of the 1,1-dibromo-1-alkene, a successful Suzuki coupling was reported by Roush et al. (see: Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541).

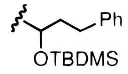
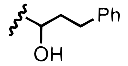
Table 1. Palladium-Catalyzed Hydrogenolysis of 1,1-Dibromo Alkenes with Tributyltin Hydride

entry	dibromoalkene		reaction time(min)	Z-bromoalkene[a]		yield[b] (%)
1	**1a**		60	**2a**		72
2	**1b**		15	**2b**		74
3	**1c**		40	**2c**		82
4	**1d**		30	**2d**		88
5	**1e**		60	**2e**		69
6	**1f**		15	**2f**		63

[a] Geometric purities were determined to be greater than 98% by ^{1}H NMR. [b] Isolated yields.

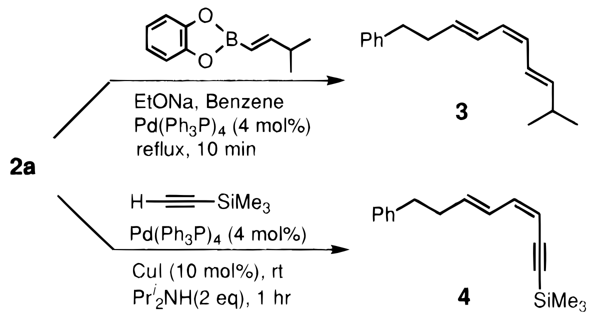
Table 2. Preparation of Enediynes 5a−c in One Pot



enediyne	R	R'	time (min)[a]	yield (%)[b]
5a	TMS	Ph	10	85
5a	Ph	TMS	10	70
5b	Ph		15	64
5c	Ph		60	54

[a] The second reaction. [b] Isolated yield.

Scheme 2



tempted regioselective coupling reaction of **1a** with (trimethylsilyl)acetylene, totally failed to give the diynyldiene.

The (*Z*)-1-bromo dienes obtained are versatile building blocks for the stereospecific synthesis of trienes or dienynes bearing the (*Z*)-olefin unit, which is shown in Scheme 2. A reaction of **2a** with (3-methyl-1-butenyl)boronate under the Suzuki conditions[17] afforded the corresponding (*E*,*Z*,*E*)-1,3,5-triene **3** in 85% yield, while **2a** reacted with (trimethylsilyl)acetylene to give the dienyne **4** in 93% yield.[18] As mentioned above, the effectiveness of the catalytic cycle of Pd(0) and the clean reaction conditions prompted us to examine these reactions in a one-pot process. Thus, if the remaining Pd(0) species is still active, and the (*Z*)-bromo dienes are stable, another Pd-catalyzed reaction may be possible. Furthermore, as the bromo polyenes and bromo enynes are in some cases relatively unstable,[19] it is quite a beneficial for them to be used for the successive reaction in one pot. Therefore, as soon as the hydrogenolysis of **1a** was completed, additions of (trimethylsilyl)acetylene, diisopropylamine, and CuI to the reaction mixture, followed by 60 min of stirring, completed the reaction to give **4** in 61% yield. On the other hand, the corresponding Suzuki coupling afforded **3** in 40−50% yields.[20]

Recently, (*Z*)-3-ene-1,5-diynes have received a great deal of attention.[5] Therefore, this process could be potentially valuable for their syntheses. In fact, the one-pot reaction was remarkably effective, as shown in Table 2. The Pd-catalyzed hydrogenolysis of **1e** with Bu$_3$SnH and the coupling with phenylacetylene gave **5a** in 85% yield in one pot. The same **5a** was derived from **1f** with (trimethylsilyl)acetylene in 70% yield. Both TBDMS-protected and -unprotected 3-hydroxy-5-phenyl-1-pentynes were coupled with **2f**, generated from **1f** *in situ*, to give **5b** and **5c** in 64 and 54% yields, respectively.[21]

In conclusion, we have found that Pd-catalyzed hydrogenolysis of *gem*-1,1-dibromo polyenes and enynes with Bu$_3$SnH proceeds stereoselectively to afford geometrically pure (*Z*)-1-bromo polyenes and enynes in good yields. The combination of this reaction and the Sonogashira−Castro or the Suzuki reaction is potentially useful for the covenient preparation of (*Z*)-enediynes or -polyenes by either stepwise or one-pot process.

Supporting Information Available: Experimental details and spectroscopic data for all compounds are available (7 pages).

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(17) For the typical Suzuki conditions, see: *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, 532.

(18) The Heck reaction of **2a** with methyl acrylate gave the corresponding (*E*,*E*,*E*)-trienecarboxylate under the improved conditions of Jeffrey (see: Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667).

(19) The bromo dienes and enynes gradually decompose, even when kept in a deep freezer. However, they were reasonably stable in the presence of triphenylphosphine.

(20) A terminal diene was formed as a serious byproduct in 30−40% yields under the one-pot conditions.

(21) The stepwise yields were 63% (**2f** to **5a**), 86% (**2f** to **5b**), and 90% (**2f** to **5c**).