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Pd(II)-Catalyzed Highly Regio- and Stereoselective Assembly of C−C Double Bonds: An Efficient Method for the Synthesis of 2,4-Dihalo-1,3,5-trienes from Alkynols

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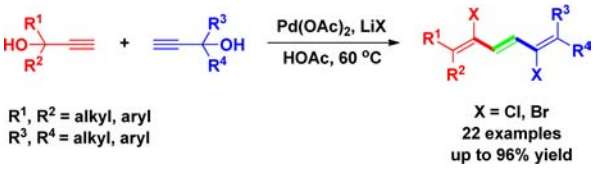
ABSTRACT



A highly efficient method for the synthesis of 2,4-dihalo-1,3,5-trienes from alkynols was developed. This chemistry allows access to multiple conjugated double bonds in a single step with high stereoselectivity.

The development of mild and efficient methods for the synthesis of complex molecular skeletons is the central focus of modern organic chemistry.[1] 1,3,5-Trienes and polyenes with their conjugated double bonds are known to be valuable synthons that have widespread application in biological chemistry, natural product synthesis and material science.[2] Consequently, the stereoselective synthesis of conjugated polyenes has attracted great attention, and a number of methods have been reported,[3] most of which are based on two types of reactions: (1) transition-metal-catalyzed cross-couplings involving Heck, Suzuki, Hiyama, Stille and Negishi reactions,[4] and (2) condensation reactions such as Wittig and Horner–Wadsworth–Emmons (HWE) olefinations.[5] Very recently, Larock et al. utilized the vinylpalladium species to react with internal alkynes to build polyene structures (Scheme 1A).[6] Meanwhile, Nagorny's group constructed polyenes through bifunctional olefin sequential condensations with aldehydes under basic conditions (Scheme 1B).[7] Despite these achievements in this fascinating research area, the further development of efficient and practical procedures to

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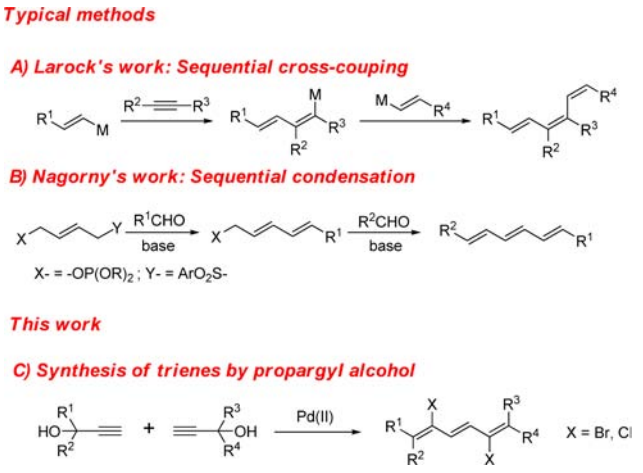
construct a 1,3,5-triene structure that minimizes the use of special reagents, cost, time and steps remains highly desirable. Herein, we disclose a highly efficient method to construct diverse 2,4-dihalo-1,3,5-trienes from propargylic alcohols, providing quick access to multiple conjugated double bonds with high selectivity in a single step (Scheme 1C). The vinyl halogen moiety in the triene products can be easily fuctionalized, thus making it a valuable synthon.[8]

As pioneered by Meyer, Schuster and Rupe,[9] propargylic alcohols are versatile synthetic reagents in synthetic organic chemistry. Apart from Meyer–Schuster and Rupe rearrangement,[10] many other elegant reactions have been developed.[11] For instance, the S_N2' displacement of propargylic compounds with organometallic reagents (Au, Rh, Zr, etc.) is one of the most commonly used methods to prepare allenes.[12] In analogy to this method, we have reported a palladium-catalyzed method to prepare allenes from propargylic alcohols,[13] in which the allenes were presumed to be generated directly through β-OH elimination. As part of our ongoing research program on the utilization of propargylic alcohols as a practical and versatile alkenylation reagent,[14] in this work, we focus on the possibility of constructing multisubstituted polyenes using these readily available starting materials.

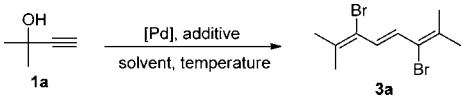
Scheme 1. Strategies for the Synthesis of Trienes



Our initial efforts were made to evaluate the palladium catalysts for the nucleopalladation of 2-methylbut-3-yn-2-ol (**1a**) to synthesize (*E*)-3,6-dibromo-2,7-dimethylocta-2,4,6-triene (**3a**) with LiBr as the additive. As shown in Table 1, Pd(II)-catalysts including $Pd_2(dba)_3$ and $PdCl_2$ could afford the desired products, and $Pd(OAc)_2$ proved to be optimal (entries 1–3). The solvent was found to have a dramatic impact on the efficiency of the reaction (entries 3–8). Notably, HOAc was identified as the most suitable medium for the formation of **3a** (entry 3). Among the various additives examined, LiBr gave the best result (entry 3, 9, 10). Plus, the optimal reaction temperature appeared to be 60 °C. Higher or lower reaction temperatures just led to a decrease in the yield. However, there was a significant increase in the yield when prolonging the reaction time to 8 h, and the desired product was obtained in 96% GC yield. The presence of phosphine ligands inhibited this chemical process (entries 11–12). Thus, **1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), LiBr (1 mmol), and HOAc (2 mL) as solvent at 60 °C were chosen as the optimized conditions.

Under these optimized reaction conditions, the reaction was applied to a range of substrates. A wide variety of *tert*-propargylic alcohols successfully afforded the corresponding 2,4-dibromo-1,3,5-triene derivatives (Scheme 2). This transformation proceeded smoothly with high stereoselectivity and afforded the single *E*-type configuration

Table 1. Optimization of Reaction Conditions for the Synthesis of (*E*)-3,6-Dibromo-2,7-dimethy-locta-2,4,6,-triene from **1a**[a]



entry	[Pd]	additive	solvent	yield[b] (%)
1	$PdCl_2$	LiBr	HOAc	85
2	$Pd_2(dba)_3$	LiBr	HOAc	80
3	**$Pd(OAc)_2$**	**LiBr**	**HOAc**	**96 (93)**
4	$Pd(OAc)_2$	LiBr	Toluene	37
5	$Pd(OAc)_2$	LiBr	CH_3CN	trace
6	$Pd(OAc)_2$	LiBr	DMF	n.d.
7	$Pd(OAc)_2$	LiBr	DMSO	n.d.
8	$Pd(OAc)_2$	LiBr	Dioxane	15
9	$Pd(OAc)_2$	$CuBr_2$	HOAc	79
10	$Pd(OAc)_2$	NH_4Br	HOAc	12
11[c]	$Pd(OAc)_2$	LiBr	HOAc	56
12[d]	$Pd(OAc)_2$	LiBr	HOAc	18

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), Pd-catalyst (5 mol %), LiBr (1 mmol) in indicated solvent (2 mL) at 60 °C for 8 h. [b] Determined by GC using dodecane as the internal standard. Data in parentheses are the yield of isolated product. n.d. = not detected. [c] Phosphorus ligand dimethylbis-diphenylphosphinoxanthene (10 mol %) was added. [d] Phosphorus ligand 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (10 mol %) was added, and 3-bromo-3-methylbut-1-yne was the main product.

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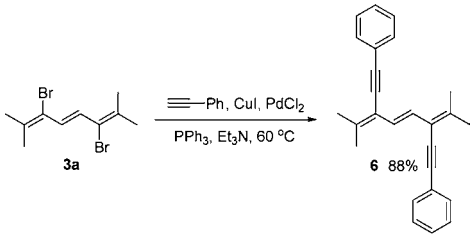
products in moderate to excellent yields for those alkynols substituted with the same groups ($R^1 = R^2$). For example, the reaction of 2-methylbut-3-yn-2-ol (**1a**) or 3-ethylpent-1-yn-3-ol (**1b**) led to the corresponding products **3a** and **3b** in 93 and 92% isolated yields, respectively. Notably, cycloalkane substituted alkynols **1d**, **1e** could also be transformed to the desired products **3d**, **3e**. In the cases where R^1 and R^2 were different, the reaction could still proceed in high isolated yields, but only the formation of the central double bond was stereospecific. Interestingly, when one of the substituents is an aromatic group, the reaction afforded a single regioisomer (all *E*-type configuration) with a slight decrease in yield. The stereochemistry of **3l** and **3n** was determined by ^{1}H NMR and NOESY spectra.[15] Moreover, this transformation was compatible with alkynols that contained Cl- and Br-substituted aryl rings, which could be used for further transformations. The electronic effects of the substituents on the phenyl were also tested. A series of *para*-substituted 2-phenylbut-3-yn-2-ols, including some with electron-donating groups (−OMe, −Me) and some with electron-withdrawing groups (−F, −Cl, −Br), were converted into the corresponding trienes, and the alkynols bearing electron-donating groups afforded lower yields since acetophenone became the main products (**3l**−**p**).

Importantly, unsymmetrically substituted trienes could also be constructed using this general and efficient method. It is particularly worthy that these unsymmetrical products also showed high stereoselectivity. Further, the aromatic groups of these unsymmetric products (**3q**−**v**) are specifically in the *trans* position of the bromine atoms. The stereochemistry of **3v** was further confirmed by ^{1}H NMR and NOESY spectra.[15]

To our delight, this method could be successfully applied to the synthesis of 2,4-dichloro-1,3,5-trienes when switching the additive from LiBr to $CuCl_2 \cdot 2H_2O$. Both the alkyl- and aryl-subsituted alkynols could be transferred to the desired trienes in good isolated yields (75−85%) with high stereoselectivity (Scheme 3).

To investigate the synthetic utility of the products, we further studied the Sonogashira coupling[16] of dihalo-1,3,5-triene compounds with terminal alkynes. Treatment of **3a** with phenylacetylene afforded 88% yield of the target product **6**, which may be a useful intermediate in opto-electronic materials.[17] The X-ray crystallographic analysis of **6** further confirmed the *E*-configuration of the triene products.[15]



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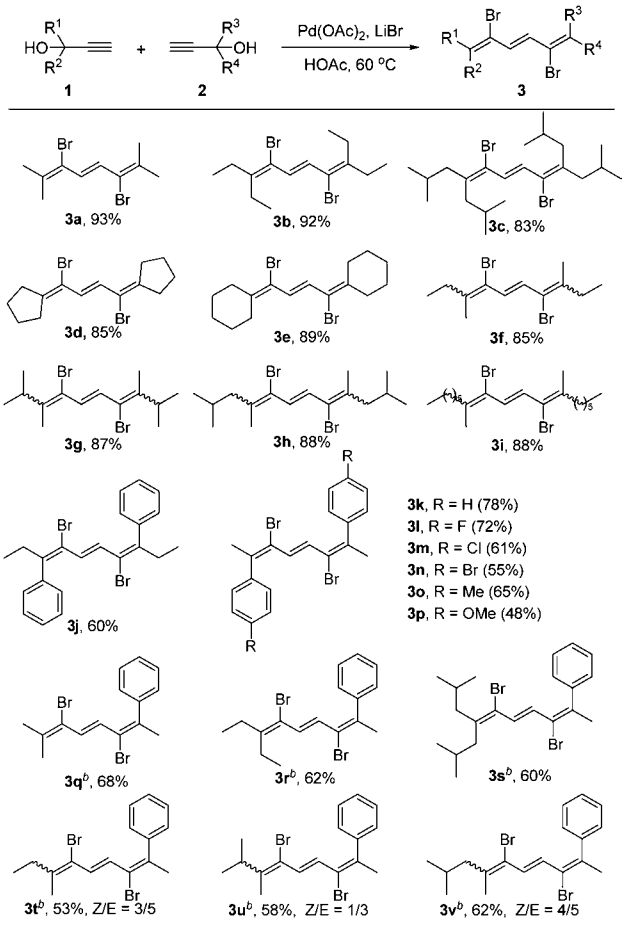
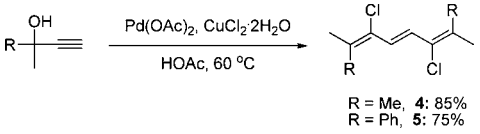
(15) See the Supporting Information for details.

Scheme 2. Pd(II)-Catalyzed Synthesis of 2,4-Dibromo-1,3,5-triene Derivatives from Alkynols[a]



[a] The reactions were carried out at 60 °C, using alkynols (0.5 mmol), LiBr (1 mmol), $Pd(OAc)_2$ (5 mol %) in HOAc (2 mL) for 8 h. Yields refer to the isolated yields. [b]Alkyl-substitute alkynol (0.25 mmol) and aryl-substituted alkynol (0.5 mmol) were used. The ratios of isomers (**3f**−**3i**) were listed in the Supporting Information, and the *Z*/*E* ratios of **3t**−**3v** were determined by GC or NMR.

Scheme 3. Formation of 2,4-Dichloro-1,3,5-trienes Derivatives



Control experiments demonstrated that no reaction occurred in the absence of Pd(II)-catalyst, and the acidic condition created by acetic acid could promote this process. Next, two deuterated experiments were carried out

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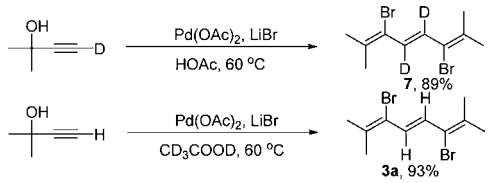
Scheme 4. Control Experiments



to distinguish the hydrogen position of the terminal alkyne. As depicted in Scheme 4, deuterium product **7** was obtained exclusively in 89% isolated yield, and the deuterium atom (98% examined by ^{1}H NMR spectroscopy) was still present. However, when deuterated acetic acid was used as the solvent, there was no deuterium in the product. Furthermore, when −OH was protected by −OAc, the desired product could not be detected in the reaction system under the standard conditions, indicating that −OH played an important role in the success of the transformation.

On the basis of the above results, a plausible mechanism involving *trans*-halopalladation and coordinative insertion is proposed, as shown in Scheme 5. The first step involves π-coordination of the carbon−carbon triple bond of **1** to the Pd(II) species followed by *trans*-halopalladation to afford vinylpalladium intermediate **II**.[18] In this process, the chelation of the hydroxyl group to the Pd(II) center improves the stereo- and regioselectivities of *trans*-halopalladation.[19] Then, the carbon−carbon multiple bond of alkynols coordinative insertion into carbon−palladium bond in the vinylpalladium intermediate occurs to yield the diene **III**, which will undergo β-OH elimination to give the allene intermediate **IV** with the aid of HOAc.[12] Finally, nucleophilic attack of bromide ion to the allene moiety of **IV** generates the desired 1,3,5-triene products.[20]

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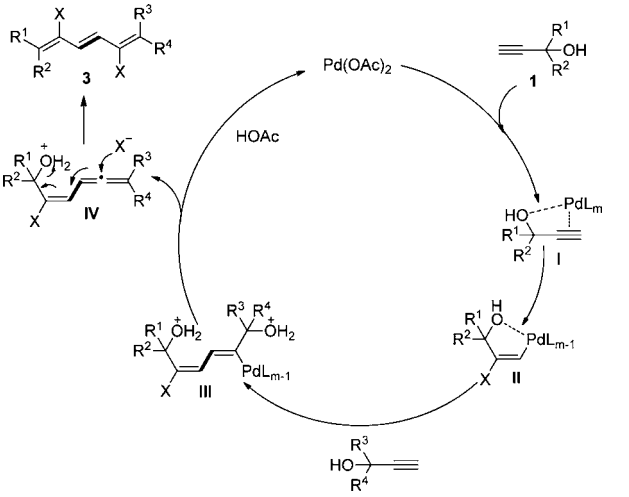
Scheme 5. Possible Reaction Mechanism



In conclusion, we have developed a general and efficient method for the synthesis of dihalosubstituted-1,3,5-triene derivatives from alkynols in a one-pot manner. The high regio- and stereoselectivity and tolerance for a range of functional groups as well as the mild reaction conditions and good to excellent yields make the present protocol very attractive. The reaction scope, detailed mechanism, and synthetic applications are under investigation in our laboratory, and the results will be reported in due course.

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Supporting Information Available. Typical experimental procedure, crystal data (CIF), and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.