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Stereodivergent synthesis of 2-alkynyl buta-1,3-dienes using Sonogashira coupling with controllable retention or inversion of olefin geometry

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ABSTRACT

Article history: Received Received in revised form Accepted Available online A stereodivergent approach to 2-alkynyl buta-1,3-dienes from a single stereoisomer of starting α -bromoenal has been developed. By simply switching the sequence of Sonogashira and Horner-Wadsworth-Emmons reactions, it is possible to obtain these branched dienynes with retention or almost complete inversion of the double bond configuration.

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Keywords: Sonogashira coupling 2-Alkynyl buta-1,3-dienes Vinyl halides Stereodivergent synthesis

The Pd/Cu-catalyzed cross-coupling of vinyl halides or pseudohalides with terminal alkynes (Sonogashira reaction) is the most straightforward and reliable method for the preparation of isomerically pure conjugated enynes. The high efficiency, mild reaction conditions and operational simplicity of this reaction have contributed to the rapid development of the chemistry of simple enynes and enediyne anticancer antibiotics, but there are only a few examples of its use for the synthesis of branched unsaturated compounds.¹

One of the interesting and little-known classes of enynes are 2-alkynyl buta-1,3-dienes, which are useful diene components in Diels-Alder reactions² and key structural motifs of advanced π conjugated polymers and chromophores.³ There are several examples of the synthesis of these compounds based on Pdcatalyzed alkenylation of 2-bromo(triflato)-1,3-enynes.⁴ The formation of branched dienyne skeleton by the reaction of some thiophosphates with sodium acetylides was reported.⁵ Shi synthesized a series of 2-alkynyl buta-1,3-dienes by the reaction of 1,1-disubstituted 2,4-diiodobut-1-enes with alkynes in the presence of Pd(PPh₃)₄/CuI catalytic system or only CuI.⁶ The Pd(PPh₃)₄-catalyzed decarboxylation of buta-2,3-dienyl 2'alkynoates allows the rapid construction of 2-alkynyl buta-1,3dienes.7 The formation of these compounds by Ru-catalyzed cross-metathesis of 1.3-divnes with 1-octene has also been described.⁸ More recently, the approach to 2-alkynyl buta-1,3dienes based on Rh-catalyzed homocoupling reaction of yalkylated tert-propargylic alcohols has been developed.9

There are very few examples of the synthesis of 2-alkynyl buta-1,3-dienes by Sonogashira cross-coupling of 2-halo-1,3-butadienes with alkynes. These include the reactions of 6-hydroxy(bromo)-substituted (3Z)-2-iodohexa-1,3-dienes with phenylacetylene,¹⁰ the reaction of [(3Z,5E)-4-bromodeca-3,5-

dien-1-yl]benzene with trimethylsilylacetylene,4b as well as the reactions of 4-alkynyl-substituted 2-iodo-1,3-butadienes and (2Z,4E)-3-iodo-5-(trimethylsilyl)penta-2,4-dienoic acid derivatives with a number of terminal alkynes.¹¹ It was reported that these reactions proceed with retention of configuration, as expected for Sonogashira reaction. However, for cross-coupling reactions of 2-halo-1,3-butadienes, which have an extended π system and are simultaneously vinylic and allylic, retention of configuration is not obligatory. Experience has shown that a cross-coupling involving 2-halo-1,3-butadienes can lead to an unexpected stereochemical result. The most well-known example is the Pd-catalyzed Negishi cross-coupling of 2-bromo-1,3butadienes with various organozinc compounds, proceeding with retention or clean stereoinversion of the Br-bearing C=C bond depending on the type of ligand used.¹² Here, we report on the synthesis of novel 2-alkynyl-1,3-butadienes via Sonogashira coupling with retention and unusual inversion of the double bond configuration.

First, we developed an efficient method for the synthesis of these compounds using a one-pot sequence Sonogashira coupling/Horner-Wadsworth-Emmons (HWE) olefination. The Pd/Cu-catalyzed cross-coupling of (2Z)-2-bromo-3-phenylprop-2-enal **1a** with oct-1-yne smoothly proceeded in the presence of PdCl₂(PPh₃)₂, CuI and diisopropylamine in MeCN to give the corresponding enyne aldehyde. Its in situ olefination with triethyl phosphonoacetate in the presence of LiCl (Masamune-Roush conditions) proved to be optimal for the efficient formation of dienyne **2aa** (Table 1). The choice of diisopropylamine and MeCN as common base and solvent is key to the success of the one-pot reaction. The organic bases commonly used in the Masamune-Roush olefination (DBU, DIPEA¹³ and Et₃N¹⁴) gave

toluene) retarded the olefination.





^aReaction conditions: 1 (0.71 mmol), alkyne (0.85 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), *i*-Pr₂NH (2.84 mmol) in MeCN (2 ml) under argon at rt for 5 h, then (EtO)₂P(O)CH₂CO₂Et (1.07 mmol), LiCl (1.07 mmol) at rt for16 h. ^bIsolated yield by column chromatography.

one-pot reaction proceeded with The complete Estereoselectivity of the newly formed C=C bond and expected retention of configuration of the Br-bearing double bond to produce single (2E,4Z)-isomer, as confirmed by NMR spectroscopy. The 2E configuration was established on the basis of the large coupling constant (J = 15.2 Hz) of the vinylic protons. The 4Z geometry was determined on the basis of NOESY correlation between H-3 and the benzylidene proton, as well as the lack of correlation between H-3 and the orthoaromatic proton (Figure 1). It is interesting to note that carrying out this one-pot reaction with a mixture of isomers of 1a (Z/E = 55:45) led to a similar stereochemical result. It is unclear, however, whether the fast inversion of thermodynamically unstable (E)-1a isomer¹⁵ occurs under the reaction conditions, or isomerization takes place within the Sonogashira catalytic cycle.



Figure 1. Assignment of dienyne configuration by NOESY correlations

investigated in this one-pot sequence. In all cases, the corresponding dienynes were obtained as pure (2E,4Z)-isomers **2ba-2ga** with good yields (63-86%), with the exception of dienyne **2ha** (yield 22%) obtained from *N*,*N*-dimethylprop-2-yn-1-amine (Table 1). (2*Z*)-2-Bromo-3-arylprop-2-enals bearing both electron-donating (OMe, **1b**) and electron-withdrawing (NO₂, **1c**) groups at the para position of the phenyl ring were tolerated and gave the corresponding products **2ia**, **2ja** in 63-67% yields.

Next, the possibility of synthesizing 2-alkynyl buta-1,3-dienes from the same starting materials using the reverse sequence HWE olefination/Sonogashira coupling was investigated. HWE reaction of aldehyde **1a** with triethyl phosphonoacetate under standard Masamune-Roush conditions (DBU, LiCl) provided (2E,4Z)-4-bromo-5-phenylpenta-2,4-dienoate **3a** in high yield (85%) and complete *E*-stereoselectivity. The Sonogashira coupling of **3a** with oct-1-yne in the presence of PdCl₂(PPh₃)₂, CuI and diisopropylamine in MeCN was not stereospecific and gave a mixture of isomers with a slight predominance of the inversion product (2E,4Z/2E,4E = 44:56) (Table 2). The 4Egeometry was established on the basis of NOESY correlation between H-3 and the *ortho*-aromatic proton, as well as the lack of correlation between H-3 and the benzylidene proton (Figure 1).

Table 2. Optimization of Sonogashira coupling of 2-bromo-1,3-butadiene **3a** with oct-1-yne^a



^aReaction conditions: **3a** (0.36 mmol), oct-1-yne (0.43 mmol), Pd-catalyst (5 mol %), ligand (10 mol %), CuI (10 mol %), *i*-Pr₂NH (1.08 mmol) in a specific solvent (2 mL) under argon at rt. ^bDetermined by ¹H NMR analysis of the crude reaction mixture. ^cIsolated yield of **2ab** as a mixture of 2*E*,4*Z* and 2*E*,4*E* isomers by column chromatography. (d) 40 °C.

Assuming that the driving force of the isomerization is steric crowding created by the proximity of phenyl group and phosphine-ligated palladium moiety in the oxidative addition complex (or subsequent species of the catalytic cycle), we tested several bulky ligands in this reaction. The monophosphines with large cone angles such as P(o-Tol)₃ or XPhos promoted the preferential formation of the inversion product (2E,4E)-2ab and unfortunately significantly reduced the rate of the cross-coupling reaction. However, subsequent investigation of the solvent effect revealed that the degree of Z/E isomerization strongly depends on the polarity of the solvent. The (2E, 4Z)-isomer was the main reaction product when using THF as solvent, whereas in more polar solvents such as DMA nearly complete inversion was observed with formation of (2E, 4E)-isomer (Table 2). Thus, by simply switching the sequence of Sonogashira and Horner-Wadsworth-Emmons reactions, it is possible to obtain 2-alkynyl

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the double bond configuration. To our best knowledge, this is the first example of the preparation of both individual *E* and *Z* enyne isomers from a single stereoisomer of vinyl electrophiles using Sonogashira reaction. It should be noted that significant reverse isomerization of the (2E, 4E)-isomer into the (2E, 4Z)-isomer was observed during the purification by column chromatography on silica gel, neutral alumina or even deactivated silica gel. Therefore, we had to determine the 2E, 4Z/2E, 4E ratio of the crude **2ab** by ¹H NMR spectroscopy and the isolated yield (as a mixture of 2E, 4Z and 2E, 4E isomers) by column chromatography (see Supporting Information).

 Table 3. Synthesis 2-alkynyl buta-1,3-dienes by Sonogashira

 coupling of 2-bromo-1,3-butadiene 3 with alkynes^{a,b,c}



^aReaction conditions: **3** (0.36 mmol), alkyne (0.43 mmol), Pd(PPh₃)₂Cl₂ (5 mol %), CuI (10 mol %), *i*-Pr₂NH (1.08 mmol) in DMA (2 ml) under argon at rt for 5 h. ^b2*E*,4*Z*/2*E*,4*E* ratio of the crude **2** by ¹H NMR spectroscopy. ^cIsolated yield (as a mixture of 2*E*,4*Z* and 2*E*,4*E* isomers) by column chromatography. ^dReaction time was 2 h. ^eReaction time was 6 h.

Using DMA as a solvent, the same series of functionalized alkynes were allowed to react with bromodiene 3a. In all cases, the Sonogashira couplings proceeded with almost complete

dienynes **2bb-2hb** in good yields (64-82%), including the reaction with challenging *N*,*N*-dimethylprop-2-in-1-amine (Table 3). The cross-coupling of electron-rich ethyl (2E,4Z)-4-bromo-5-(4-methoxyphenyl)penta-2,4-dienoate **3b** with oct-1-yne to form dienyne **2ib** was somewhat faster than that of either unsubstituted **3a** or electron-poor nitro-substituted bromodiene **3c**. This is the opposite of the general reactivity trend of substituted aryl electrophiles in the Sonogashira coupling.^{1a} It is also interesting that the stereoselectivity of the formation of methoxy-substituted dienyne **2ib** was as high as that of unsubstituted **2ab** (95 % 2E,4E), while in the case of nitro-substituted dienyne **2jb** it was significantly lower (83% 2E,4E) (Table 3).

Next, we tested the effect of the conjugated carbonyl group, which is believed to contribute to the isomerization of the C=C bond through resonance.¹⁶ The sequence including Sonogashira coupling of (2*Z*)-2-bromo-3-phenylprop-2-enal **1a** with 3,3-dimethyl-1-butyn and subsequent Wittig reaction of the resulting enyne aldehyde with methylenetriphenylphosphorane gave dienyne **2ka** as a single (*Z*)-isomer in low overall yield. The reverse sequence Wittig reaction/Sonogashira coupling led to the predominant (although not so impressive) formation of the inversion product **2kb** (*E*/*Z* = 82:18) (Scheme 1). Thus, a key requirement for the inversion in the Sonogashira coupling is the presence of a C=C bond conjugated with the Br-bearing C=C bond. This is consistent with the observed stereochemistry in the Negishi cross-coupling of 2-bromo-1,3-butadienes.¹²



Scheme 1. Switching the sequence of Sonogashira and Wittig reactions

Finally, some aspects of the isomerization mechanism were considered. It is clear that the inversion occurs along the Sonogashira catalytic cycle, since no significant isomerization was observed during prolonged stirring of 2-bromo-1,3-butadiene 3a or dienyne 2aa in MeCN in the presence of all reagents [Pd(PPh₃)₂Cl₂, CuI, diisopropylamine] except the alkyne. The Z/E isomerization in cross-coupling reactions of simple vinyl halides has been reported in several studies. The liganddependent isomerization mechanisms within the cross-coupling catalytic cycle have been proposed for the loss of stereochemistry in Suzuki-Miyaura,¹⁷ Stille¹⁸ and Negishi¹⁹ reactions. More recently, the extensive isomerization in Suzuki cross-couplings of haloenones was explained by a separate Pd-catalyzed isomerization process.²⁰ However, for 2-halo-1,3-butadienes, bearing a halogen at the vinylic and allylic position simultaneously and thus capable of both vinylic and allylic type Pd-catalyzed transformations, the isomerization mechanism may be even more complicated. The observed stereoinversion may be due to the relative thermodynamic stabilities of various possible alkylidene- π -allylpalladium species.^{12a} Similar complexes were isolated and characterized by NMR spectroscopy and X-ray crystallography.²¹ However, the inversion mechanism involving such intermediates should be different from the widely accepted π - σ - π rearrangement of simple allylpalladium derivatives, which requires a double Z/E stereoinversion (Scheme 2).



Scheme 2. Double Z/E stereoinversion via π - σ - π rearrangement

The loss of Z geometry may occur via a zwitterionic palladium carbene species (with either an anionic or cationic benzylic carbon), which can be considered as real intermediates or resonance structures (Scheme 3). Such dipolar intermediates were first proposed to explain the isomerization of cisvinylrhodium complexes.²² Later, this mechanism was used to explain the stereochemistry of formal anti-carbopalladation^{16b,23} and other metallocatalyzed additions to alkynes,²⁴ as well as cross-coupling reactions involving simple vinyl electrophiles.¹⁷⁻¹⁹ From the steric point of view, the trans relationship between the aryl group and the bulky phosphine-ligated Pd moiety should be thermodynamically more favorable than the initial Z configuration. This mechanism is partly supported by the beneficial effect of polar solvents such as DMA capable of stabilizing zwitterionic intermediates on the formation of the inversion product. The rapid conversion of methoxy-substituted bromodiene 3b and anomalously low stereoselectivity of the formation of nitro-substituted dienyne 2jb are also in agreement with the positive charge buildup on the benzylic carbon. Other isomerization mechanisms via η²-vinylpalladium metallacyclopropene species are also possible.24b,25



Scheme 3. Isomerization via a zwitterionic palladium carbene species

In summary, we have developed an efficient method for the stereodivergent synthesis of 2-alkynyl buta-1,3-dienes using Sonogashira and Horner-Wadsworth-Emmons reactions. By simply switching the sequence of these reactions, it is possible to obtain 2-alkynyl buta-1,3-dienes with retention or almost complete inversion of the double bond configuration. This approach to the control of stereochemistry could be useful in stereoselective synthesis of branched enynes, especially when only a single isomer of starting vinyl halides (pseudohalides) is available.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at:

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Highlights

- Stereodivergent synthesis of branched dienynes
- Preparation of both individual *E* and *Z* enyne
- isomers using Sonogashira coupling
- Almost complete inversion in Sonogashira coupling
- High isomeric purity

