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New Zirconium-Mediated Approach Toward Regio- and Stereocontrolled Synthesis of *trans*-Enediynes

Yuanhong Liu* and Hongjun Gao

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

yhliu@mail.sioc.ac.cn

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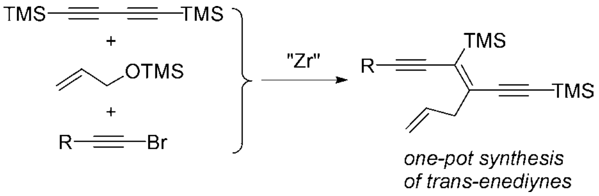
ABSTRACT



The coupling reactions of α-alkynylated zirconacyclopentene based on 1,4-bis(trimethylsilyl)-1,3-butadiyne with unsaturated compounds are described, which provide an efficient, regio- and stereocontrollable synthesis of *trans*-enediynes in a one-pot procedure. An interesting alkynyl group shift from α- to *β*-position of the zirconium center during the reaction was observed, which was accountable for the novel transformations to *trans*-enediynes.

Enediynes (hex-3-ene-1,5-diynes, DEEs) represent important building blocks for the construction of π-conjugated polymers and designed nanoarchitectures, which have attracted much interest due to their wide applications as advanced materials with unique electronic and photonic properties such as in molecular wires, switches, organic conductors, polyelectrochromic materials, and light-emitting diodes, etc.[1] Especially, oligomers having an enyne or enediyne scaffold with an olefin substituent would greatly enhance the solubility of the materials, which permits investigation and modification of their structural and electronic properties.[2] As a consequence, much attention has been paid to the synthesis of enediyne derivatives. Metal-catalyzed cross coupling between alkenyl halides and terminal acetylenes or metal acetylides provides one of the most versatile routes for enediynes.[3] The stereochemical outcome of the reaction is highly dependent on the experimental conditions and the substituents on the alkene groups. The preparation of (*Z*) and/or (*E*)-DEEs could also be achieved by elimination of a silanol from α-silyl alcohols,[4] a carbenoid coupling elimination strategy,[5] acid- or base-induced elimination of alcohols,[6] alkyne metathesis,[7] or Pd-catalyzed dimerization,[8] etc.[9]

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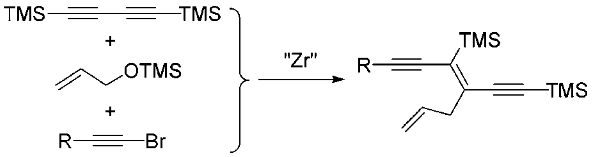
Nevertheless, the development of new protocols that allow stereoselective and one-pot synthesis of enediynes from readily available precursors is highly attractive. In this paper, we report novel zirconium-mediated coupling reactions of three different components involving 1,4-bis(trimethylsilyl)-1,3-butadiyne, allylic ether, and alkynyl bromide in a one-pot procedure, which provide an efficient regio- and stereocontrollable synthesis of *trans*-enediynes (Scheme 1).

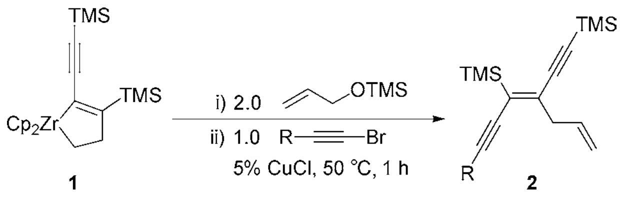
Scheme 1



The organometallic complexes of diynes R(C≡C)$_2$R and polyynes R(C≡C)$_n$R with group 4 metallocenes have attracted considerable attention owing to their fascinating structural features, their unique M−C bonding, and their unusual capacity to induce highly selective transformation reactions.[10] Takahashi et al. reported that the reaction of 1,3-butadiynes with a zirconocene−ethylene complex gave zirconacyclopentenes bearing an alkynyl substituent exclusively at the α-position.[11] Zirconacyclopentenes are known to undergo cross-coupling reactions with unsaturated compounds through a facile β,β'-carbon−carbon bond cleavage reaction along with elimination of one ethylene molecule.[12] Thus, the behavior of zirconacyclopentenes can be viewed as a zirconocene−alkyne complex. In an attempt to achieve coupling reactions of α-alkynylated zirconacyclopentenes with elimination of ethylene,[13] we observed the *trans*-enediyne formation reaction.

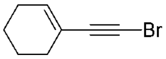
Reactions of conjugated diyne with $Cp_2Zr(CH_2{=}CH_2)$ in situ prepared from Cp_2ZrEt_2 gave α-alkynylzirconacyclopentenes, which afforded dideuterated enyne after deuteriolysis and α-alkynylcyclopentenones by treatment with CO/I$_2$.[11b] In the case of diaryldiynes, a reductive elimination proceeded upon heating or in the presence of DMAD.[11c] Here, we found that treatment of zirconacycle **1** derived from disilyldiyne with an excess amount (2 equiv) of allyloxytrimethylsilane[13b] at 50 °C followed by the reaction with alkynyl bromide[14] (1.0 equiv) in the presence of a catalytic amount of CuCl (5%) afforded *trans*-enediyne **2** smoothly in good to excellent yields (Scheme 2).

Scheme 2



The representative results are listed in Table 1. A number of aryl-substituted (electron-deficient and electron-rich aromatics) alkynylation agents could be incorporated successfully into the sequence. The corresponding enediynes were obtained in 63−98% yield.

Table 1. Formation of *trans*-Enediynes

entry	R—≡—Br	product	yield%[a,b]
1	p-$NO_2C_6H_4$—≡—Br	(**2a**)	98 (62)
2	p-MeC_6H_4—≡—Br	(**2b**)	90 (76)
3	p-ClC_6H_4—≡—Br	(**2c**)	85 (67)
4	p-$MeOC_6H_4$—≡—Br	(**2d**)	73 (60)
5	2,6-diClC_6H_3—≡—Br	(**2e**)	76 (73)
6	C_6H_5—≡—Br	(**2f**)	65 (60)
7	p-$CF_3C_6H_4$—≡—Br	(**2g**)	63 (61)
8	CO_2Et—≡—Br	(**2h**)	93 (61)
9	n-Bu—≡—Br	(**2i**)	75 (70)
10		(**2j**)	89 (71)

[a] GC yield; isolated yields are in parentheses. [b] All the reactions were carried out at 50 °C for 1 h.

The functionalities of NO_2, Cl, MeO, and CF_3 groups in the aromatic ring were tolerated during the reaction, affording the corresponding products **2** in good to high yields (Table

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(13) To the best of our knowledge, there is no report concerning the coupling reaction of α-alkynylated zirconacyclopentenes with elimination of ethylene. For the carbon−carbon bond formation reaction of alkyl- or aryl-substituted zirconacyclopentenes via elimination of ethylene molecule, see: (a) Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871. (b) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* **1994**, *35*, 5685. (c) Takahashi, T.; Kondakov, D. Y.; Suzuki, N. *Tetrahedron Lett.* **1993**, *34*, 6571. (d) Takahashi, T.; Kondakov, D. Y.; Suzuki, N. *Chem. Lett.* **1994**, 259.

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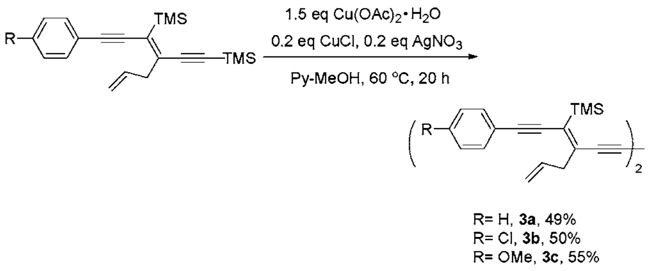
1, entries 1, 3−5, and 7). The present method worked well with butyl-, cyclohexenyl-, or ester-substituted alkynyl bromides, furnishing the products **2g**−**2j** in 75−93% yields (Table 1, entries 8−10).

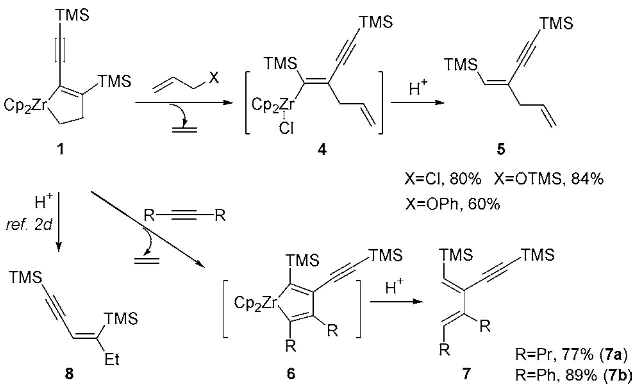
The stereochemistry of *trans*-enediyne was unambiguously established by X-ray single-crystal analysis of an enediyne dimer **3c** (Scheme 3) which was prepared by desilylation of **2d** followed by an oxidative Hay coupling[15] with a total yield of 61%. It was shown that the unique enediyne framework facilitates π-conjugation with aromatic substituents by allowing coplanar orientation throughout the molecular core. We have also developed a convenient one-flask synthesis of conjugated diynes **3** by combination of Ag$^+$-catalyzed desilylation[16] and Eglinton−Glaser coupling[17] reactions. Under the optimized reaction conditions, the ethynyltrimethylsilanes **2f**, **2c**, and **2d** were converted directly to butadiynes, affording the corresponding products **3a**−**c** in 49−55% yields.

Scheme 3



To elucidate the reaction mechanism, we carried out the coupling reactions of zirconacycle **1** with allylic compounds without the addition of alkynyl bromide (Scheme 4). Surprisingly, product **5** was obtained as a >98% isomerically pure enyne derivative in which a C−C bond formation occurred exclusively at the vinylic carbon substituted with an alkynyl[18] group rather than with a TMS group. The result indicates that an interesting alkynyl group shift from α- to β-position with relation to the zirconium center during the reaction occurred to afford allyl zirconation intermediate **4**. In the presence of 1 equiv of 4-octyne, zirconacyclopentadiene **6a** was formed. After hydrolysis, a 1,3-butadiene derivative **7a** was obtained in 77% yield as a single regioisomer. Diphenylacetylene did not give a high yield of zirconacyclopentadiene in THF; however, results improved considerably with a change of solvent from THF to toluene, which increased the yield of **7b** to 89% at 80 °C for 1 h. In both cases, no homocoupling products of the alkynes were observed.

Scheme 4



These results clearly demonstrate that the formation of the zirconocene−butadiyne complex proceeded via a β,β'-C−C bond cleavage reaction at higher temperature, which could direct regioselective olefin or alkyne coupling by locating a silyl group at the α-position of a zirconacycle intermediate.[19] We believe that both electronic (trialkylsilyl groups are known to stabilize α-carbanions)[19] and steric factors are responsible for the regiochemical outcome of the coupling reactions. The mechanism for allylation of the zirconocene−butadiyne complex to give **4** is similar to that found in allyl zirconation reactions using zirconocene−alkyne complexes.[13] Thus, the *trans*-enediynes **3** were formed by the coupling reactions of alkynyl bromides with intermediate **4** in the presence of CuCl.

In conclusion, we have developed an efficient and selective synthesis of *trans*-enediynes from 1,3-butadiyne precursors. This methodology allows for the ready synthesis of *trans*-enediynes with different substituents in the central double bond that are difficult to prepare by other available procedures. Clarification of the reaction mechanism and utilizing this and related methodologies for the synthesis of π-conjugated polymers will be the subject of future reports.

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Supporting Information Available: Experimental details and spectroscopic characterization of all isolated compounds and CIF files giving crystallographic data of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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