

Stereoselective Synthesis of β -Hydroxyallenes with Multiple Contiguous Stereogenic Centers via Aldehyde Addition to α -Alkenyl-Substituted Zirconacyclopentenes

Yebing Zhou, Jingjin Chen, Chunbin Zhao, Erjuan Wang, Yuanhong Liu,* and Yuxue Li*

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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A highly stereoselective methodology for the synthesis of β -hydroxyallenes with multiple stereogenic centers including allenic axial chirality, as well as center chirality, via addition of α -alkenylzirconacyclopentenes to aldehyde is described. Remarkably, the reaction occurs with completely different chemoselectivity in comparison with the usual alkyl- or aryl-substituted zirconacyclopentenes; that means, the C–C bond formation occurred selectively at the alkenylic carbon substituted with phenyl or alkyl group, while in the latter cases, insertion of aldehydes into the alkyl–zirconium bond to afford seven-membered oxazirconacycles has usually been observed.

Introduction

The development of a new reaction process for stereoselective synthesis of complex molecules with multiple stereogenic centers in one flask occupies an important place in organic synthesis.^{1,2} Allenes, especially functionalized allenes, are of current interest since they serve as versatile synthetic intermediates for a wide range of transformation reactions; they are also useful for

asymmetric synthesis by transferring their axial chirality to one or several centered chiralities.^{3–5} Although a number of methods for the stereoselective construction of allenes with two stereogenic centers have been reported,⁶ such as S_N2' ring-opening

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^{*}To whom correspondence should be addressed. Fax: (+86) 021-64166128.

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SCHEME 1



80%

of propargylic epoxide with organocuprate or Grignard rea-gent,^{6c,6d} or copper-catalyzed additions of organometallic nucleophiles to β -lactones, ^{6e} those for three or more than three are quite rare. One of the elegant syntheses of such compounds is that reported by Sato et al.;⁷ they have described a stereoselective addition of unsaturated compounds including aldehydes or imines to an enyne-titanium alkoxide complex, which created up to three new stereodefined carbon centers. However, according to their report, the addition of aldehyde to a three-membered titanacyclopropene usually gave rise to a mixture of two isomeric alcohols.⁷ In this paper, we report a direct insertion of aldehyde to α -alkenyl-substituted zirconacyclopentenes, which provides a new and convenient procedure for the concise construction of multisubstituted β -hydroxyallenes with high levels of stereocontrol. It turned out that one of the diastereomers with high purity out of the four possibilities arising from two contiguous stereogenic centers and an adjacent allenic axial chirality could be obtained after chromatography.

 C_5H_{11}

3a. trace

(1a)

Results and Discussion

It is known that the coupling of an alkyl-substituted conjugated envne such as 3-ethyl-oct-3-en-5-yne with a zirconocene-ethylene complex⁸ affords five-membered zirconacyclopentene with high regioselectivity, which means that the alkenyl substituent is located on the α -position of a zirconacycle.9 However, the synthetic utilities of these zirconacycles have not been pursued. Our recent success in the highly stereoselective synthesis of cis-[3]cumulenols via zirconium-mediated coupling of 1,3-butadiynes with aldehydes or ketones¹⁰ and our continued interest in metallacycles¹¹ prompted us to explore the new synthetic potential of α -functionalized zirconacycles toward carbon electrophiles. Here we found that treatment of conjugated (E)-envne non-1-en-3-ynyl-benzene 1a with a zirconocene-ethylene complex in THF at room temperature selectively generated α -alkenylzirconacyclopentene 2a with only trace amounts of its regioisomer of α -alkylzirconacycle **3a** according to crude NMR (Scheme 1), which afforded the stereodefined diene product of (1E,3Z-4-ethylnona-1,3-dienyl)benzene 4a in 80% yield after hydrolysis. The interaction of the alkenyl moiety in the α -position with the zirconium center may contribute to the high regioselectivity. It was also found that addition of 1 equiv of *p*-chlorobenzaldehyde to zirconacycle **2a** at room temperature for 5 h furnished β -hydroxyallene **5a** smoothly in 63% yield after hydrolysis. To our surprise, the C-C bond formation occurred selectively at the alkenvlic carbon substituted with a phenyl group. The chemoselectivity in this case is in marked contrast to that observed with alkyl- or aryl-substituted zirconacyclopentenes, since insertion of aldehydes into the alkyl-zirconium bond to afford seven-membered oxazirconacycles has usually been observed.¹² The behavior of α -alkenylzirconacycle 2 toward aldehyde addition is similar to that of α -alkynyl-substituted zirconacyclopentenes as we reported recently,¹⁰ in which the alkynylic moiety reacted preferentially to a $Zr-C(sp^3)$ bond. The product 5a has two contiguous stereogenic centers and an adjacent allenic axial chirality. It is interesting to note that only one diastereomerically pure allene 5a out of the four possible diastereoisomers was isolated. Careful analysis of the crude reaction mixture through ¹H NMR spectra revealed that there exists a small amount of another diastereoisomer, the ratio of **5a** with this diastereomer being 93:7. This result indicated a high degree of stereoselectivity was achieved in this reaction. To make clear the relative stereochemistry of 5a, we proceeded to make the crystals of the

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TABLE 1. Stereoselective Formation of β -Hydroxyallenes with Multiple Stereogenic Centers



entry	R ¹	R ²	R ³ CHO	product	yield(%) ^a
1	<i>n</i> -C ₅ H ₁₁	Ph	p-CIC ₆ H₄CHO	5a	63 (93:7)
2	<i>n</i> -Pr	Ph	3,4,5-(MeO) ₃ C ₆ H ₂ CHO	5b	68 (93:7)
3	<i>n</i> -C₅H ₁₁	Ph	p-CH ₃ C ₆ H ₄ CHO	5c	68 (97:3)
4	<i>n</i> -C ₅ H ₁₁	Ph	p-NMe ₂ C ₆ H ₄ CHO	5d	72 ^b (93:7)
5	<i>n</i> -C ₅ H ₁₁	Ph	PhCHO	5e	58 (97:3)
6	<i>n</i> -C ₅ H ₁₁	Ph	p-NO ₂ C ₆ H ₄ CHO	5f	67 (88:12)
7	<i>n</i> -C ₅ H ₁₁	Ph	СНО	5g	53 (96:4)
8	<i>n</i> -C ₅ H ₁₁	Ph	"PrCHO	5h	63 (98:2)
9	<i>n</i> -Pr	Ph	1-naphthaldehyde	5i	65 (96:4)
10	<i>n</i> -Pr	Ph	p-NO₂C ₆ H₄CHO	5j	71 (89:11)
11	<i>n</i> -Pr	Ph	<->− CHO	5k	65 (96:4)
12	p-Ru	n-Ru	ⁿ PrCHO	51	630

^{*a*}Yield of the isolated pure major isomer after chromatographic separation on silica gel. The diastereomeric ratio of two isomers determined by the ¹H NMR of the crude reaction mixture is shown in parentheses. All the reactions were carried out at room temperature for 3-6 h. ^{*b*}Containing two diastereomers, the ratio is 98:2. ^{*c*}Containing two diastereomers, the ratio is 98:5.

resulting β -hydroxyallenes or its derivatives. However, most of the products were isolated as oily compounds. After much effort, we were delighted to find that an allene product **5b**, derived from the reaction of zirconacyclopentene **2b** with 3,4,5-trimethoxybenzaldehyde (Table 1, entry 2), formed a good quality of crystals which were suitable for X-ray analysis.¹³ X-ray crystallography of these crystals unambiguously verified the stereochemistry of β -hydroxyallene **5**. The configuration of **5b** was assigned as $(1R^*, 2S^*, R^*_a)$ -**5b**. Thus the same $(1R^*, 2S^*, R^*_a)$ -configuration of **5a** was deduced from the result of **5b**.

Similarly, addition of zirconacycle prepared from (Z)-enyne 6^{14} to *p*-chlorobenzaldehyde proceeded to afford a mixture of two diastereoisomers with a lower stereoselectivity (5.5:1)







SCHEME 4



compared with that of (*E*)-enyne (Scheme 2). The configuration of the major isomer was assigned to be $(1R^*, 2R^*, R^*_a)$ -**5a** according to X-ray crystallographic analysis.¹³ The minor isomer was found to be identical with $(1R^*, 2S^*, R^*_a)$ -**5a** as indicated by NMR analyses.

Oxidation of $(1R^*, 2S^*, R^*_a)$ -5a by DMP followed by reduction using NaBH₄ afforded the two diastereoisomers of 5a in 25% and 58% yields, respectively (Scheme 3, eq 1). The assignment of the relative stereochemistry of $(1S^*, 2S^*,$ R^*_{a})-5a is based on X-ray crystallographlic study.¹³ This result indicated that the isomers were formed only at the alcoholic stereogenic carbon during the reaction. The same reaction starting from $(1R^*, 2R^*, R^*_a)$ -5a afforded a mixture of $(1R^*, 2R^*, R^*_a)$ -5a and $(1S^*, 2R^*, R^*_a)$ -5a (Scheme 3, eq 2). Thus, all of the four diastereoisomers of 5a could be obtained, which enabled us to understand the diastereoselectivity of the addition reaction well. By comparison of the ¹H and ¹³C NMR of a crude sample shown in Scheme 1 and the isolated diastereomers, the minor diastereoisomer formed in the reaction mixture of *p*-chlorobenzaldehyde was assigned to be $(1S^*, 2S^*, R^*_a)$ -5a.

The present allene-formation procedure has proved to be applicable to substituted enynes with various aldehydes, both aromatic and aliphatic, as shown in Table 1. First, we examined the electronic effect of substitution on the aldehyde aromatic ring. Virtually no significant differences in the reaction yields have been observed with electron-withdrawing or electron-donating substituents on the aromatic ring. The corresponding β -hydroxyallenes were obtained in

⁽¹³⁾ The X-ray crystal structures of $(1S,2R,S_a)$ -**5b**, $(1R,2R,R_a)$ -**5a** and $(1R,2R,S_a)$ -**5a** are shown in the Supporting Information. Note: The X-ray structure of $(1S,2R,S_a)$ -**5b** and $(1R,2R,S_a)$ -**5a** has the *ent*-configuration of the assigned configuration of $(1R^*,2S^*,R^*_a)$ -**5b** and $(1S^*,2S^*,R^*_a)$ -**5a**.

⁽¹⁴⁾ Hydrolysis of the reaction mixture of the zirconocene–ethylene complex with (Z)-enyne **6** afforded a mixture of several alkene isomers that could not be separated. The mechanism of this hydrolysis experiment was not clear yet.



FIGURE 1. The optimized transition structures with selected bond lengths (in angstroms). Their relative Gibbs free energies are in kcal/mol. Calculated at the $B3LYP/6-311+G^{**}/Lanl2DZ$ level.

SCHEME 5



58-72% yields as a single isomer after separation in most cases (Table 1, entries 1-6). The functionalities of -Cl, -NMe₂, and -NO₂ groups on the phenyl ring were well tolerated during the reaction, affording the corresponding products 5a, 5d, and 5f in good yields (63-72%), entries 1, 4, and 6). However, p-nitrobenzaldehyde afforded lower selectivities (entries 6 and 10). Heteroaryl aldehydes such as 2-thienyl aldehyde could be incorporated successfully into the sequence, the corresponding allene being obtained in 53% yield (entry 7). When a bulky substrate such as 1-naphthaldehyde was used, the reaction proceeded to afford 5i in a yield of 65% (entry 9). Interestingly, the use of 4-(phenylethynyl)phenyl aldehyde afforded 5k in 65% yield, in which the alkyne moiety remained intact (entry 11). Bisalkyl-substituted enyne also proceeded smoothly to afford product 51 in 63% yield (entry 12). When a ketone such as acetophenone was used instead of aldehydes, only a slight reaction occurred. It should be noted that when zirconacycle $2e^9$ derived from trisubstituted envne (Z)-4-ethyldec-4-en-6vne was used for the reaction, the allene 5m was isolated as a single isomer in 54% yield (containing small amount of byproducts), the stereochemistry has not been defined yet (Scheme 4).

On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 5. In the first step, the aldehyde approaches the Zr center by coordination of its carbonyl oxygen with the metal. This is followed by a S_E2' -type¹⁵ reaction at the allylzirconium moiety via a six-membered transition state 7, yielding a nine-membered oxazir-concycle 8 with a cyclic allenic structure. Hydrolysis of 8 affords the desired β -hydroxyallene 5. To understand the

mechanism, the reaction mixture of **2a** with *p*-chlorobenzaldehyde was investigated by NMR experiment. The NMR study of the resulting mixture indicated the formation of a major diastereomer of **8a** ($R^1 = C_5H_{11}$, $R^2 = Ph$, $R^3 =$ *p*-ClC₆H₄) in 77% NMR yield (Scheme 5), and its structure is in good agreement with the proposed oxazirconacycle **8**. The ¹H NMR of **8a** in C₆D₆/THF solution shows two singlets at 5.87 and 5.92 ppm, and its ¹³C NMR spectrum reveals two singlets at 110.7 and 110.8 ppm, which are assigned to Cp ligands. The low-field signal (204.3 ppm) is characteristic for sp carbon in the allene skeleton.

To understand the stereoselectivity of this reaction (Scheme 1), density functional theory (DFT) studies have been performed with the Gaussian03 program¹⁶ by using the B3LYP¹⁷ method. For C, H, and O, the 6-311+G** basis set was used; for Zr, the Lanl2DZ basis set with Effective Core Potential (ECP)¹⁸ was used. Harmonic vibration frequency calculation was carried out and the optimized structures are all shown to be transition states with one imaginary

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frequency. In the calculation models, $R^1 = Me$, R^2 and $R^3 = Ph$. The results are shown in Figure 1.

The results show that the configuation of the favorable transition states of *E*-enyne product $(Ts-(1R^*, 2S^*, R^*_a))$ is consistent with that of the experimental products. In this transition state, the 4C-O-Zr six-membered ring is in a stable *chair* conformation, whereas in $Ts-(1S^*, 2S^*, R^*)$ the 4C-O-Zr six-membered ring is in an unstable boat conformation. The relative stabilities of $Ts-(1R^*, 2S^*, R^*_a)$ and Ts- $(1S^*, 2S^*, R^*_a)$ may be understood this way: if the position of the phenyl group and the hydrogen atom of the aldehyde are exchanged in Ts-(1R*,2S*,R*a), we get Ts-(1S*,2S*, R^*_{a}). Obviously, if the 4C-O-Zr six-memberd ring still keeps its *chair* conformation, the phenyl group of the aldehyde will eclipse with the Cp ring. Therefore the 4C-O-Zr six-membered ring must be deformed to avoid this large steric effect. Therefore, the stereoselectivity of this reaction originates mainly from the steric effect of the phenyl group of the aldehyde and the Cp ring. However, the stereochemical course for (Z)-enyne 6 is unclear at this time.

Conclusion

In summary, we have developed an efficient zirconiummediated stereoselective formation of allenes with multiple stereogenic centers under mild reaction conditions. Remarkably, the addition of α -alkenylzirconacyclopentenes to aldehydes occurred with complete chemoselectivity, in which the allylzirconium moiety reacted preferentially to a Zr–C(sp³) bond. The resulting β -hydroxyallenes are well suited for further manipulation, as demonstrated recently¹⁹ by the diastereoselective formation of pyrans via gold-catalyzed cycloisomerizations.

Experimental Section

Formation of the Diene 4a from the Reaction of the Zirconocene–Ethylene Complex with (*E*)-Enyne 1a. To a solution of Cp_2ZrCl_2 (0.183 g, 0.625 mmol) in THF (5 mL) was added EtMgBr (1.0 M THF solution, 1.25 mmol) at ca. -50 °C. After the mixture was stirred for 1 h at the same temperature, (*E*)-non-1-en-3-ynylbenzene (0.099 g, 0.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then quenched with 3 N HCl and extracted with ethyl acetate. The extract was washed with water and brine and dried over Na₂SO₄. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel (petroleum ether). Diene **4a** was formed in 80% (91 mg) isolated yield as a colorless oil. (**1***E*,**3***Z***-4-Ethylnona-1,3-dienyl)benzene (4a):** ¹H NMR (CDCl₃, Me₄Si) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 7.8 Hz, 3H), 1.26–1.50 (m, 6H), 2.14 (q, *J* = 7.5 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 6.01 (d, *J* = 10.8 Hz, 1H), 6.46 (d, *J* = 15.3 Hz, 1H), 7.04 (dd, *J* = 15.3, 10.8 Hz, 1H), 7.15–7.20 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.38–7.40 (m, 2H); ¹³C NMR (CDCl₃, Me₄Si) δ 12.7, 14.1, 22.6, 28.6, 30.1, 31.0, 31.9, 123.8, 125.5, 126.0, 126.8, 128.5, 129.9, 138.1, 146.6; HRMS (EI) calcd for C₁₇H₂₄ 228.1878, found 228.1877.

A General Procedure for the Stereoselective Construction of β-Hydroxyallenes via the Reaction of α-Alkenylzirconacyclopentenes with Aldehydes. To a solution of Cp₂ZrCl₂ (0.183 g, 0.625 mmol) in THF (5 mL) was added EtMgBr (1.0 M THF solution, 1.25 mmol) at ca. -50 °C. After the mixture was stirred for 1 h at the same temperature, (E)-enyne (0.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 2 h. Aldehyde (0.5 mmol) was added and the mixture was stirred at room temperature for 3-6 h. The reaction mixture was then quenched with 3 N HCl and extracted with ethyl acetate. In the case of the reaction with 4-(dimethylamino)benzaldehyde, the reaction mixture was quenched with water. The extract was washed with water and brine and dried over Na₂SO₄. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to afford β -hydroxyallene derivative 5. (1R*,2S*,R*a)-1-(4-Chlorophenyl)-5-ethyl-2-phenyl-deca-3,4-dien-1-ol (5a): Purification by flash chromatography on silica gel (eluent: petroleum ether: $EtOAc: Et_3N = 91:8:1$) afforded the title compound in 63% isolated yield. ¹H NMR $(CDCl_3, Me_4Si) \delta 0.80 (t, J=6.9 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H),$ 1.20–1.31 (m, 6H), 1.89–1.97 (m, 4H), 2.74 (s, 1H), 3.46 (t, J= 7.8 Hz, 1H), 4.79 (d, J=8.1 Hz, 1H), 5.45-5.50 (m, 1H), 7.02-7.21 (m, 9H); ¹³C NMR (CDCl₃, Me₄Si) δ 12.3, 13.9, 22.4, 25.6, 27.2, 31.5, 32.5, 55.7, 77.0, 92.2, 108.2, 126.6, 127.8, 127.9, 128.2, 128.3, 132.7, 140.3, 140.8, 201.3; HRMS (EI) calcd for C24H29OCl 368.1907, found 368.1893.

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Supporting Information Available: General methods and spectroscopic characterization of all new compounds and CIF files giving crystallographic data of compounds $(1S,2R,S_a)$ -**5b**, $(1R,2R,R_a)$ -**5a**, and $(1R,2R,S_a)$ -**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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