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Stereoselective hydrozirconation of alkynylsulfide and regioselective synthesis of haloalkenyl sulfide via electrophile-switched halogenation of thioalkenyl zirconocene

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ABSTRACT

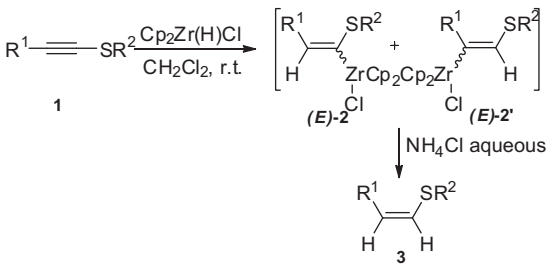
Stereoselective preparation of alkenyl sulfide was carried out via *syn*-hydrozirconation of the alkynyl sulfide. Regiochemistry of halogenation of the thioalkenyl zirconocene could be switched by different halides. α-Chloroalkenyl sulfide or β-haloalkenyl sulfide (Br, I) could be obtained by the treatment of NCS or NBS (NIS), respectively. Possible mechanism of halogenation of the thioalkenyl zirconocene was set up herein.

Alkenyl sulfides are ubiquitous in the nature, which are widespread with therapeutic properties[1] and regarded as the significant synthetic intermediates for their attractive reactivity.[2] Generally, the synthesis of the alkenyl sulfide could be performed by the cross-coupling of alkenyl halide with thiols in the presence of various catalysts.[3] Hydrothiolation[4] of alkyne using catalysts has been exploited to access alkenyl sulfide, which configured the *syn*-[5] or *anti*-addition[6] depending on the type of the involved transition-metal-catalyst or stoichiometric amount of the Lewis acid. Recently, Ying and co-workers have proved that the stereoselectivity of copper-catalyzed hydrothiolation could be determined by the presence/absence of a CO_2 atmosphere.[7] Palladium-catalyzed *syn*-thioboration of terminal alkynes also leads to alkenyl sulfide.[8]

In addition, the reduction of alkynyl sulfide to alkenyl sulfide is quite limited.[9] As we know, hydrozirconation of functionalized alkyne[10] followed by halogenation[10c–e] plays an important role in the synthesis of functionalized alkenyl halide, which could lead to the formation of polysubstituted alkene. To the best of our knowledge, electrophilic substitution of alkenyl zirconocene usually positions on the sp^2 carbon attached to the zirconium atom so far.[10]

In most cases, the *syn*-hydrozirconation of internal alkynes with heteroatomic groups, such as chalcogenides,[11] ZnX,[12] BR_2,[13] SnR_3,[14] SiR_3,[15] I^+R_2[16]etc., provide α-heteroalkenyl zirconocene as the major product. However, the behaviors of alkynyl sulfone or sulfoxide are abnormal owing to a *trans*-hydrozirconation and the generation of β-heteroalkenyl zirconocene,[17] which actuated us to study on the chemistry of the alkynyl sulfide which also carries C–S bond in the molecular. Therefore, we now wish to report the chemistry of hydrozirconation of alkynylsulfide. Furthermore, as useful intermediates to prepare structure-defined alkenes,[18] haloalkenyl sulfides will be produced via regioselectively electrophile-switched halogenation of thioalkenyl zirconocene.

To the suspension of Schwartz's reagent ($Cp_2Zr(H)Cl$, 1.2 mmol) in CH_2Cl_2 was added 1.0 equiv of alkynyl sulfide **1** at room temperature. The reaction mixture was then stirred till a clearly khaki solution of *(E)*-thioalkenyl zirconocene **2** was obtained. Hydrolysis of **2** with saturated ammonium chloride aqueous afforded *(Z)*-alkenyl sulfide **3a**–**i** in moderate to good yields (Scheme 1).[19] The results are listed in Table 1.



Scheme 1. Preparation and hydrolysis of *(E)*-thioalkenyl zirconocene **2**.

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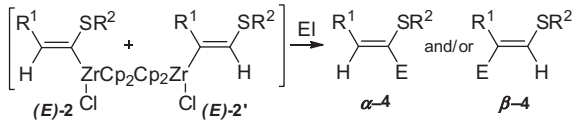
According to the $^3J_{H-H}$ between the two vinyl protons in product **3** (Table 1), all of the coupling constants are less than 12 Hz, which indicated the *Z* configuration of the product **3**. The investigation of ^{1}H NMR spectra of the crude products **3** showed the purity of *(Z)*-isomer was above 99%. That is, the hydrozirconation of alkenyl sulfide underwent selectively a *syn*-addition.

To determine the regiochemistry of the hydrozirconation, the *in situ* prepared *(E)*-thioalkenyl zirconocene **2** in CH_2Cl_2 was quenched with 1.0 equiv of other electrophiles at 0 °C and gave the corresponding trisubstituted alkenyl sulfide **4** (Scheme 2).[20] The results are listed in Table 2.

With the treatment of DCl or NCS, the α-substituted products **4a**–**h** were generated in moderate to good yield. Owing to the coupling and splitting data in the ^{1}H NMR spectra of the products, the regiochemistry of **4a**–**h** are similar to the results of the literatures (entries 1–8 in Table 2).[11–16] Surprisingly, bromination or iodination of **2** chiefly gave *β*-substituted alkenyl sulfide (entries 9–17 in Table 2). Based on the same substrates (entry 5 and entry 10), the regiochemistry of chlorination of **2** was contrary to that of the bromination. Therefore, regiochemistry of halogenation of the thioalkenyl zirconocene could be switched by different halides. *(E)*-1-chloroalkenyl sulfide or *(E)*-2-haloalkenyl sulfide (Br, I) could be obtained by treatment of NCS or NBS (NIS), respectively.

As to the formation of the α- or *β*-haloalkenyl sulfides, a possible mechanism was hypothesized as follows (Scheme 3).[11a] *(E)*-Thioalkenyl zirconocene **2** was generated from the hydrozirconation of the alkynyl sulfide **1** followed by another addition of $Cp_2Zr(H)Cl$ to **2** to result in α,*β*-dizirconium species **5**. There achieved an equilibrium between the two intermediates of *(E)*-**2** and **5** in this reactive system. Compound **5** was readily converted into *(E)*-**2** by *syn*-elimination with release of $Cp_2Zr(H)Cl$ because the empty orbital in sulfur atom could stabilize the carbon anion attached to zirconium. While Cl^+ or D^+ was addressed in the reaction, the stabilized carbon anion could undergo electrophilic substitution as well as *syn*-elimination of $[Zr]^2$–H^2 to afford α-**4** (path a in Scheme 3). *β*-SR^2 elimination with $[Zr]^2$ would occur to lead to *(Z)*-alkenyl zirconium **6**, which was the probable reason why the yields of **4a**–**h** (entries 1–8 in Table 2) were lower than those of *β*-bromides (**4i**–**m**) or iodides (**4n**–**q**). The chlorinated product **7** was detected by GCMS.[21] In the case of Br^+ or I^+, it was a rigorous challenge for the larger size of the electrophiles to attack the sterically hindered α-C with two bulky groups, thioalkyl and zirconium. Thus *β*-anion of **5** was engaged in and underwent a *syn*-elimination of $[Zr]^1$–H^1 to give *β*-**4**.

The in situ NMR of the mixture of the hydrozirconation of alkynyl sulfide (R^1 = *n*Bu, R^2 = *n*Pr) was carried out (Fig. 1). Compound **5** and *(E)*-**2** were detected in the ratio of 63:37 as well as a trace amount of *(E)*-2′. As to compound **5**, the C–H correlation spectroscopy showed two dt peaks at 5.50 (*J* = 7.5, 5.8 Hz, H^1) and 5.82 (*J* = 7.5, 1 Hz, H^2) ppm assignable to the two protons, respectively. In the species

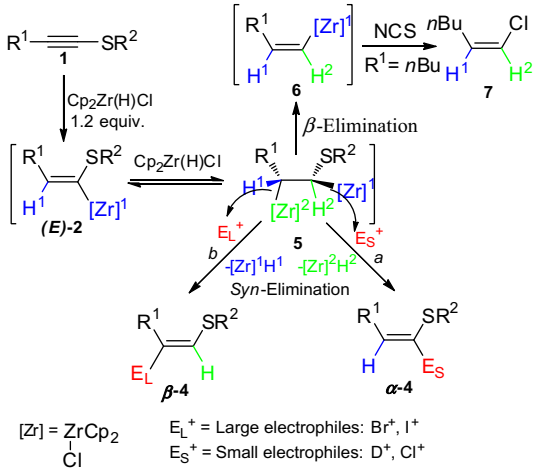


Scheme 2. Reaction of *(E)*-thioalenyl zirconocene **2** with electrophiles.

Table 2
Reaction of *(E)*-**2** with electrophiles

Entry	R^1	R^2	Reagents	α-**4**:*β*-**4**[a]	Yield of 4[b] (%)
1	*n*Bu	*n*Pr	DCl/$D_2$0	>99:1	56 (**4a**)
2	*n*Bu	*n*Bu	DCl/$D_2$0	>99:1	48 (**4b**)
3	*n*Hex	*n*Pr	DCl/$D_2$0	>99:1	52 (**4c**)
4	*n*Hex	*n*Bu	DCl/$D_2$0	>99:1	47 (**4d**)
5	*n*Bu	*n*Pr	NCS	>99:1	48 (**4e**)
6	*n*Bu	Bn	NCS	94:6	55 (**4f**)
7	*n*Bu	*n*Bu	NCS	>99:1	52 (**4g**)
8	*n*Hex	*n*Bu	NCS	>99:1	57 (**4h**)
9	*n*Bu	Et	NBS	<1:99	85 (**4i**)
10	*n*Bu	*n*Pr	NBS	<1:99	90 (**4j**)
11	*n*Bu	*n*Bu	NBS	<1:99	78 (**4k**)
12	*n*Hex	*n*Pr	NBS	12:88	88 (**4l**)
13	*n*Hex	*n*Bu	NBS	<1:99	68 (**4m**)
14	*n*Bu	Et	NIS	<1:99	89 (**4n**)
15	*n*Bu	Bn	NIS	10:90	85 (**4o**)
16	*n*Hex	Et	NIS	22:78	82 (**4p**)
17	*n*Hex	Bn	NIS	26:74	79 (**4q**)

[a] Ratio of α-**4**:*β*-**4** is based on the ^{1}H NMR spectra of the crude products of the reactions.
[b] Isolated yields.



Scheme 3. Mechanism of formation of thioalkenyl sulfide **2** and its regioselective halogenation.

Table 1
Synthesis of *(Z)* alkenyl sulfide **3**

Entry	R^1	R^2	^{1}H NMR of α-H to thio group	Yield of **3**[a] (%)
1	*n*Bu	Et	5.91 (d, $^3J_{H-H}$ = 9.2 Hz, 1H)	72 (**3a**)
2	*n*Bu	*n*Pr	5.89 (d, $^3J_{H-H}$ = 9.6 Hz, 1H)	68 (**3b**)
3	*n*Bu	iPr	5.89 (d, $^3J_{H-H}$ = 9.6 Hz, 1H)	54 (**3c**)
4	*n*Bu	*n*Bu	5.90 (d, $^3J_{H-H}$ = 9.2 Hz, 1H)	62 (**3d**)
5	*n*Bu	Ph	6.19 (d, $^3J_{H-H}$ = 9.2 Hz, 1H)	59 (**3e**)
6	*n*Hex	*n*Pr	5.89 (d, $^3J_{H-H}$ = 9.6 Hz, 1H)	65 (**3f**)
7	*n*Hex	*n*Bu	5.91 (d, $^3J_{H-H}$ = 9.2 Hz, 1H)	61 (**3g**)
8	Ph	*n*Pr	6.43 (d, $^3J_{H-H}$ = 10.8 Hz, 1H)	60 (**3h**)
9	Ph	Bn	6.42 (d, $^3J_{H-H}$ = 11.2 Hz, 1H)	66 (**3i**)

[a] Isolated yields.

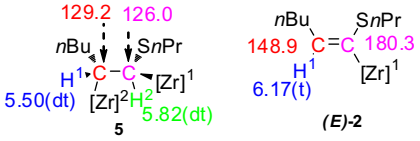
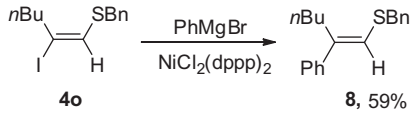


Figure 1. In situ NMR data of the mixture of hydrozirconation.

(E)-**2**, the sp^2 carbon attached zirconium atom appeared characteristically at 180.3 ppm and the other sp^2 carbon at 148.9 ppm.[22]

When alkynyl sulfide (R^1 = *n*Bu, R^2 = *n*Pr), Schwart's reagent, and NBS were mixed together according to the comments of the re-



Scheme 4. Selective conversion of β-haloalkenyl sulfide.

viewer, a mixture of β-bromoalkenyl sulfides **4j** and α-product in the ratio of 90:10 was obtained based on the NMR of crude product. Initially, before the excess amount of $Cp_2Zr(H)Cl$ was consumed, the ratio of α-thioalkenyl zirconocene **2** in Scheme 3 was higher than that after accomplishment of hydrozirconation. It was a favorable opportunity for bromination of α-position. Along with the processing of the hydrozirconation, the amount of dizirconium species **5** would increase to result in the formation of β-bromoalkenyl sulfides **4j**. Thus β-bromoalkenyl sulfides dominated and the results of this reaction were quite similar with our former study. Therefore, the formation of **5** via second hydrozirconation of the species **2** followed by *syn*-elimination of $[Zr]^1H^1$ could be concluded.

Owing to two functional groups in the molecule, the iodoalkenyl sulfide **4o** was involved in the $NiCl_2(dppp)_2$ catalyzed cross-coupling reaction to give C–I bond cleavage product **8** in the isolated yield of 59% and the C–S bond was reserved selectively (Scheme 4).[23] Therefore, the two functional groups could be converted stepwisely, which could be utilized to prepare a polysubstituted alkene.

It was reported that hydrozirconation of internal alkynyl chalcogenides (Se, Te) in THF mainly gave the α-zirconated alkenyl chalcogenide intermediates, in which 2.0 equiv of $Cp_2Zr(H)Cl$ was crucial to perform the total hydrozirconation of alkynyl selenides or tellurides.[11] In the case of alkynyl sulfide, only 1.2 equiv of $Cp_2Zr(H)Cl$ was enough to complete the reaction. Moreover, dichloromethane rather than THF was favorable for the reaction of alkenyl sulfide with acceptable yield and regio- or stereoselectivity. The chemistry of **2** differs from that of sele- or tellualkenyl zirconocene.

In conclusion, we have demonstrated the efficient formation of thioalkenyl zirconocene species via hydrozirconation of alkynyl sulfide, which can readily give *(Z)*-disubstituted alkenyl sulfides in good yields. Also, the regioselective synthesis of α- or β-haloalkenyl sulfide via electrophile-switched halogenation of thioalkenyl zirconocene has been developed, which can be regarded as the precursor for the synthesis of polysubstituted alkene derivatives. Further investigation into the reactivity of thioalkenyl zirconecene is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.122.

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19. General experimental procedure for the hydrozirconation of the alkynyl sulfide: to a suspension of $Cp_2Zr(H)Cl$ (1.2 mmol) in CH_2Cl_2 at room temperature was added alkynyl sulfide (1.0 mmol). The above reaction mixture was then stirred till to be a clearly khaki solution, which was quenched with saturated ammonium chloride aqueous followed extracted with ether for three times. The combined organic layer was washed with brine and dried over anhydrous MgSO4. After rotary evaporation, the residue was purified by column chromatograph (silica gel, hexane as the eluent) to afford *(Z)*-alkenyl sulfide **3a**–**i**.

20. General procedures for the synthesis of trisubstituted alkenyl sulfide **4**: at 0 °C, the solution of in situ prepared *(E)*-thioalkenyl zirconocene **2** in CH_2Cl_2 was quenched with 1.0 equivalent of DCl/D_2O (for **4a**–**d**), NCS (1.2 mmol, 0.16 g for **4e**–**4h**), NBS (1.2 mmol, 0.21 g for **4i**–**4m**) and NIS (1.2 mmol, 0.27 g for **4n**–**4q**), respectively and extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After rotary evaporation, the residue was purified by column chromatograph (silica gel, hexane as the eluent) to afford **4a**–**q**.
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