Article

Studies on the Regio- and Stereoselectivity of Halohydroxylation of 1,2-Allenyl Sulfides or Selenides

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It was observed that the halohydroxylation of 1,2-allenyl sulfides or selenides with Br₂ (CuBr₂ or NBS) or I₂ and water demonstrated a fairly good regioselectivity (i.e., the C=C bond that is remote from the S or Se atom was halohydroxylated with the halogen atom connecting to the middle carbon atom and the hydroxyl group connecting to the non-S terminal carbon or Se-substituted terminal carbon atom of the allene moiety), leading to the synthesis of synthetically important 3-organosulfur or seleno-2-haloallylic alcohols. The stereoselectivity depends on the nature of X^+ and S or Se, showing a Z-selectivity with the matched Lewis acid-base pair.

Introduction

Allenes show unique reactivity in organic synthesis due to the presence of the cumulated C=C double bonds.¹ Recently, much attention has been paid to the study on their reactivity, especially the control of the related selectivity.^{2,3} An addition reaction of a carbon-carbon multiple bond is synthetically attractive because two functional groups are introduced within one operation.⁴ However, reports on the addition reactions of allenes⁵ are limited, probably because of the problem of controlling

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the regio- and stereoselectivity.⁶ Recently, we observed the following: (1) The electron-withdrawing group of the electron-deficient allenes determines the regioselectivity of the corresponding hydrohalogenation reaction, leading to β,γ unsaturated functionalized alkenes.⁷ (2) The excellent regioselectivity and E-stereoselectivity of the iodohydroxylation reaction of 1,2-allenyl sulfoxides was determined by the participation of the sulfinyl group, because of the formation of a five-membered cyclic intermediate.8

In a preliminary communication, we have demonstrated that the iodohydroxylation reaction of 1,2-allenyl sulfides is high-yielding with excellent Z-selectivity, which is opposite to what was observed with 1,2-allenyl sulfoxides.⁹ In this paper, we wish to report the scope, regioselectivity, and stereoselectivity of the halohydroxylation of 1,2-allenyl sulfides or selenides. The combination of a different X^+ with S or Se showed that the Zselectivity may be controlled by the nature of Lewis basicity of the S or Se atom and the Lewis acidity of X⁺.

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SCHEME 1



1a, 2a: R¹ = Ph, R² = H, R³ = Bn, R⁴ = CH₃; **1b**, **2b**: $R^1 = Ph$, $R^2 = H$, $R^3 = H$, $R^4 = H$; **1c**, **2c**: $R^1 = Ph$, $R^2 = H$, $R^3 = H$, $R^4 = CH_3$; **1d**, **2d**: $R^1 = Ph$, $R^2 = H$, $R^3 = H$, $R^4 = i-Pr$; **1e**, **2e**: $R^1 = Ph$, $R^2 = H$, $R^3 = H$, $R^4 = n-C_4H_9$; **1f, 2f**: R^1 = Ph, R^2 = H, R^3 = H, R^4 = *n*-C₇H₁₅; **1g, 2g**: R¹ = Ph, R² = H, R³ = H, R⁴ = Bn; **1h**, **2h**: $R^1 = Ph$, $R^2 = H$, $R^3 = CH_3$, $R^4 = CH_3$; **1i**, **2i**: $R^1 = Ph$, $R^2 = H$, $R^3 = CH_3$, $R^4 = C_2H_5$; **1j 2j:** R¹ = Ph, R² = H, R³ = CH₃, R⁴ = *i*-Bu; **1k**, **2k**: $R^1 = Ph$, $R^2 = H$, $R^3 = CH_3$, $R^4 = t - C_4 H_9$; **11, 21:** $R^1 = Ph$, $R^2 = H$, $R^3 = C_2H_5$, $R^4 = C_2H_5$; **1m**, **2m**: $R^1 = Ph$, $R^2 = H$, $R^3 = n - C_4 H_9$, $R^4 = n - C_4 H_9$; **1n, 2n:** $R^1 = Ph$, $R^2 = H$, $R^3 = n-C_5H_{11}$, $R^4 = n-C_5H_{11}$; **10, 20:** R¹ = Ph, R² = H, R³, R⁴ = -(CH₂)₄-; **1p, 2p:** R^1 = Ph, R^2 = H, R^3 , R^4 = -(CH₂)₅-; **1q, 2q:** $R^1 = p$ -Br-Ph, $R^2 = H$, $R^3 = H$, $R^4 = n$ -C₄H₉



SCHEME 2



Results and Discussion

Synthesis of the Starting Materials. The starting 1,2-allenylic sulfides (**2**) were prepared via the reduction of 1,2-allenylic sulfoxides (**1**), which are easily available from the reaction of the readily available propargylic alcohols with PhSCl (Scheme 1).^{10,11}

1,2-Butadienyl-3-yl phenyl sulfide (**2s**) was prepared via the rearrangement of 3-phenylthio-1-butyne (eq 1).¹²

$$\begin{array}{c} PhS \\ \hline CH_3 \end{array} \xrightarrow{t-C_4H_9OK/t-C_4H_9OH} \xrightarrow{PhS} CH_3 \end{array}$$
(1)

1,2-Allenylic selenides (**4**) were prepared similarly via the rearrangement of propargyl aryl selenides (**3**) (Scheme 2).¹³

Iodohydroxylation of 1,2-Allenylic Sulfides (2). We started this research with the iodohydroxylation of



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TABLE 1. Iodohydroxylation of 1,2-Allenyl Sulfides

$\begin{array}{c} PhS \\ H \\ R^{2} \\ R^{3} \end{array}$		$R^{2} = \frac{I_{2} (2 \text{ equ})}{R^{3} \text{ acetone / } H_{2}C}$	iv) (4:1), rt	PhS I R ² HO	
	2			6	
_		2	time	yield	Z/E
try	R ²	R ³	(h)	of 6 ^a (%)	of
	Bn	CH3 (2a)	13	68 (6a)	99/

1	Bn	CH ₃ (2a)	13	68 (6a)	99/1
2	Н	Н (2b)	9	41 (6b)	99/1
3	Н	CH ₃ (2c)	9	61 (6c)	97/3
4	Н	<i>i</i> -Pr (2d)	10	56 (6d)	96/4
5	Н	<i>n</i> -C ₄ H ₉ (2e)	13.5	74 (6e) ^b	98/2
6	Н	<i>n</i> -C ₇ H ₁₅ (2f)	9.5	67 (6f) ^c	96/4
7	Н	Bn (2g)	9.5	65 (6g) ^d	96/4
8	CH_3	CH ₃ (2h)	10.5	63 (6h)	94/6
9	CH_3	C ₂ H ₅ (2i)	10	94 (6i)	94/6
10	CH_3	<i>i</i> -Bu (2j)	12	53 (6j) ^e	99/1
11	CH_3	<i>t</i> -C ₄ H ₉ (2k)	9	85 (6k)	97/3
12	C_2H_5	C_2H_5 (21)	8	72 (6l)	98/2
13	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉ (2m)	10	93 (6m)	95/5
14	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁ (2n)	10	80 (6n)	97/3

^{*a*} Unless otherwise stated, the corresponding aldehyde **5** was isolated in trace amount. ^{*b*} 14% of **5e** was isolated. ^{*c*} 18% of **5f** was isolated. ^{*d*} 18% of **5g** was isolated. ^{*e*} 14% of **5j** was isolated.

3-benzyl-1,2-butadienyl phenyl sulfide (2a) with I_2 and H₂O. When we performed the iodohydroxylation under the same reaction conditions as those for 1,2-allenyl sulfoxides,⁸ only a Z/E mixture of 2-iodo-2-propenal (5a) was formed via the intermediacy of 7a (Scheme 3), indicating a different regioselectivity with the OH group attacking the carbon atom connected with the PhS group. The configuration of the C=C bond in **5a** was determined by the NOE study. However, after some trial and error, we were pleased to note that the regioselectivity of this reaction can be reversed to a fairly high extent, leading to the formation of synthetically useful 2,3-iodohydroxylation product Z-6a in 68% yield, with 99/1 E/Z-selectivity, along with 16% yield of 5a when the reaction was conducted in aqueous acetone (acetone/ $H_2O = 4:1$) (Scheme 3).

Some typical results of the Z-iodohydroxylation of 1,2allenyl sulfides are summarized in Table 1.⁹ Z-2-Iodo-3-(organosulfur)-2-alkenols (**6**) were formed in moderateto-high yields highly stereoselectively: Both 3-mono- and 3,3-disubstituted allenyl sulfides reacted smoothly with I_2 in aqueous acetone. The stereoselectivity, which was determined by the NOE experiment of Z-**6e** and the

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SCHEME 4



 TABLE 2.
 Bromohydroxylation of 1,2-Propdienyl

 Phenyl Sulfide (2b)
 Phenyl Sulfide (2b)

PhS		[Br]		PhSBr		
	2b	solver	nt		10b	4
entry	[Br] (equiv)	solvent ^a	<i>T</i> (°C)	time (h)	yield of 10b (%)	Z/E ^b
1	CuBr ₂ (2)	4:1	15	9	34	1.83/1
2	$CuBr_2(2)$	4:1	25	7.5	39	2.88/1
3	$CuBr_{2}(10)$	4:1	25	6	30	99/1
4	NBS (2)	4:1	50	3	10	99/1
5	NBS (2)	4:1	25	9	31	99/1
6	NBS (2)	4:1	0	7	49	4.38/1
7	$Br_{2}(2)$	4:1	0	7	26	21/1
8	$Br_{2}(2)$	4:1	50	3	29	99/1
9	$Br_{2}(2)$	4:1	25	9	47	99/1
10	$Br_{2}(2)$	4:1 ^c	25	13	12	3.94/1
11	$Br_{2}(2)$	$2:2:1^{d}$	25	13	17	16/1

^{*a*} Unless otherwise noted, solvents are CH_3CN/H_2O in the volume ratio indicated. ^{*b*} The Z/E ratio determined by 300 MHz ¹H NMR spectra. ^{*c*} CH₂Cl₂/H₂O were used as the solvents. ^{*d*} MeCN/CH₂Cl₂/H₂O were used as the solvents.

oxidation of *Z*-**6e** with *m*-CPBA in CH_2Cl_2 or H_2O_2 in HOAc to the corresponding sulfoxide *Z*-**8e**,⁹ is completely opposite to that for the corresponding sulfoxides.⁸

When **20** and **2p** were used as the starting allenyl sulfides, Z-(1-iodo-2-phenylthioethenyl)cycloalkenes **90** and **9p**⁹ were formed via the dehydration of the iodohydroxylation product (Scheme 4).

Bromohydroxylation of 1.2-Allenylic Sulfides. Some typical results of the bromohydroxylation of 1,2propadienyl phenyl sulfide (2b) under different conditions are summarized in Table 2, from which it can be seen that, under similar conditions used for the halohydroxylation of allenylsulfoxides,8 the bromohydroxylation reaction of 1,2-allenyl sulfides can occur to afford 10b with different stereoselectivities when NBS, Br₂, or CuBr₂ was chosen as the halogen source. With CuBr₂, the stereoselectivity was high and the yield was as low as 30%, even with 10 equiv of $CuBr_2$ (entries 1–3, Table 2). The yield was higher when the reaction was conducted with NBS at a lower temperature, but the reaction was less stereoselective (entries 4-6, Table 2). The stereoselectivity was improved when Br2 was used, with the highest yield (10b) at 47% and a Z/E ratio of 99/1 (entry 9, Table 2). The results in other solvents were poor (entries 10 and 11, Table 2). The stereoselectivity of this reaction was established by the NOE experiment of Z-10b.

Similar results were also observed with 1,2-heptadienyl phenyl sulfide (**2e**) (entries 1-6, Table 3). It is obvious

 TABLE 3.
 Bromohydroxylation of 1,2-Heptadienyl

 Phenyl Sulfide (2e)
 Phenyl Sulfide (2e)

Ph		[Br]	F	hS	Br →─C₄H	- <i>n</i>
	0411	g	•,		нό	•
	2e				10e	
entry	[Br] (equiv)	additive (equiv)	<i>T</i> (°C)	time (h)	yield of 10d (%)	Z/E ^a
1	NBS (2)		25	12	34	27/1
2	NBS (2)		0	7	46	34/1
3	$Br_{2}(1)$		25	15	45	99/1
4	$Br_{2}(1)$		0	6	54	99/1
5	$Br_2(1.5)$		25	12	30	99/1
7	$Br_{2}(2)$		25	12	39	99/1
8	${ m Br}_{2}(2)$	$Na_2CO_3(1)$	25	10	51	99/1
9	${ m Br}_{2}(2)$	NaHCO ₃ (1)	25	6.5	52	99/1
10	${ m Br}_{2}(2)$	$K_2CO_3(1)$	25	9	50	99/1
11	${ m Br}_{2}(2)$	$LiOAc \cdot 2H_2O(1)$	25	9	41	99/1
12	${ m Br}_{2}(2)$	$Na_2CO_3(1)$	25	10	51	99/1
14	Br ₂ (2)	Na ₂ CO ₃ (1)	0	2	58	96/1
15	${ m Br}_{2}(2)$	$Na_2CO_3(1)$	-10	13	52	99/1
16	${ m Br}_{2}(2)$	$Na_2CO_3(1.5)$	0	7	46	99/1
17	${ m Br}_{2}(2)$	$Na_2CO_3(2)$	0	16	53	99/1
18	${ m Br}_{2}(2.5)$	$Na_2CO_3(1)$	0	6	45	99/1
^a Th	e Z/E ratio v	vas determined by	v 300 M	IHz ¹ H	I NMR sr	oectra

^a The Z/E ratio was determined by 300 MHz ¹H NMR spectra of the crude product.

that, in terms of both yield and stereoselectivity, the reaction proceeded more efficiently with Br_2 than with NBS (compare entries 1-2 with 3-4, Table 3). To avoid the influence of the in-situ-formed HBr on stereoselectivity, the effect of different bases on stereoselectivity was studied. The yield increased slightly when Na_2CO_3 (1 equiv) was added (entry 8, Table 3). NaHCO₃, K_2CO_3 , or LiOAc·2H₂O can also be applied (entries 9-11, Table 3). The best results were realized when the reaction was run with Br_2 (2 equiv) with the addition of Na_2CO_3 at 0 °C to afford **10e** in 58% yield and a Z/E ratio of 99/1 (entry 14, Table 3). Increasing the amount of Br_2 or base did not yield better results (entries 16-18, Table 3).

Some typical results of Z-bromohydroxylation of 1,2allenyl sulfides are summarized in Table 4, showing that both 3-mono- and 3,3-disubstituted allenyl sulfides (2) reacted smoothly with Br_2 in aqueous acetonitrile to give the products Z-10 in reasonably high yields with excellent Z-selectivity.

When 1-alkyl-substituted 1,2-allenyl phenyl sulfides $(2\mathbf{r}-\mathbf{s})$ were used, $10\mathbf{r}-\mathbf{s}$ were produced with fairly high Z/E ratios (Scheme 5).

When sulfide **2p** was treated with Br_2 in aqueous acetone, *Z*-**11p** was formed in 65% yield with a ratio of Z/E > 99/1 (Scheme 4).

Iodohydroxylation of 1,2-Allenylic Selenides. Several selenium-substituted allenes are known as isolable compounds or reactive intermediates;¹⁴ however, there is only very limited study on their reactivities.^{15,16} According to our results on allenyl sulfides, we wish to expand this reaction to 1,2-allenyl selenides. Some typical

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^{*a*} The Z/E ratio was determined by 300 MHz ¹H NMR spectra of the crude product; ^{*b*} No Na₂CO₃ was used. ^{*c*} *p*-Bromophenyl sulfide was used instead of phenyl sulfide.

SCHEME 5



2s: R¹ = CH₃,

, **10s:** (44%, *Z/E* = 36:1)

results of iodohydroxylation of 1,2-propadienyl phenyl selenide (4a) with I₂ and H₂O are summarized in Table 5. When the iodohydroxylation of 4a with I2 and H2O was carried out under the same conditions as those employed for 1,2-allenyl sulfoxides,8 the expected product (11a) was isolated in only 28% yield with a Z/E ratio of 12.5:1 (entry 1. Table 5).¹⁶ The stereoselectivity was determined unambiguously by the X-ray diffraction study of Z-11e.¹⁷ We explored the effect of the ratio of nitrile/water on the reaction. The reaction could not proceed when there was too much water in the mixed solvent (entry 10, Table 5). The stereoselectivity can be tuned by reaction temperature: The reaction at 0 °C in MeCN/H₂O (4:1) afforded 11a in 70% yield with a Z/E ratio of 99/1 (entry 18, Table 5). Some typical results of Z-iodohydroxylation of 1,2allenyl selenides are summarized in Table 6.

The bromohydroxylation of 1,2-allenyl selenides **4a**, **4b**, or **4o** with Br_2 under similar reaction conditions as those for sulfides failed to yield the expected products (**12**) (Scheme 6).

 TABLE 5. Addition Reaction of 4a with I2 under

 Different Conditions^a

Ρ	hSe	= + I ₂ —	$\xrightarrow{\text{MeCN/H}_2\text{O}} \xrightarrow{\text{PhSe}} I$			ЭН
	4a				11a	
	I_2		Т	time	yield of	
entry	(equiv)	MeCN/H ₂ O	(°C)	(h)	11a (%)	Z/E^d
1 ^b	2	7:1	21	10	28	12.5/1
2	1.2	4:1	27	5.5	26	е
3	1.5	4:1	27	5.5	49	е
4 ^c	2	4:1	-10	10.5	54	26/1
5	2	4:1	-5	10	70	41/1
6	2	4:1	0	20	68	35/1
7	2	4:1	13	17	66	13.5/1
8	2	4:1	25	15	46	22/1
9	2	1:1	9	11	37	32/1
10	2	1:4	5	11	trace	е
11	2	7:1	22	20	75	16/1
12	2	7:1	21	10	28	12.5/1
13	3	4:1	0	17	73	52/1
14	4	4:1	27	7.5	61	3.50/1
15	4	4:1	14	7	75	10/1
16	2	4:1	0	7.5	61	3.5/1
17	4	4:1	0	10.5	69	99/1
18	5	1:1	0	17.5	70	99/1

 a **4a** was added into the solution of I₂/nitrile/H₂O within a minute. b 2 equiv of LiOAc·2H₂O was used. c **4a** was added into a solution of I₂/nitrile/H₂O over 30 min. d Determined by 300 MHz $^1\mathrm{H}$ NMR spectra of the crude product. e Not determined.

TABLE 6. Iodohydroxylation of Allenyl Selenides

RSe		l ₂ (4 equiv) MeCN:H ₂ O (v/v=4:1)		RSe	
н		0°C, N ₂	-	н́с	ЭН
4				11	
			time	yield of	
entry		R	(h)	11 (%)	Z/E^a
1	Ph (4a)	1	17.5	69 (11a)	99/1
2	p-CH ₃ C	C ₆ H ₄ (4b)	20.5	72 (11b)	99/1
3	o-CH ₃ C	C ₆ H ₄ (4c)	10	72 (11c)	99/1
4	m-CH ₃	C ₆ H ₄ (4d)	19.5	74 (11d)	28/1
5	p-BrC ₆	H ₄ (4e)	19	66 (11e)	99/1
6	p-ClC ₆ l	H4 (4f)	19	72 (11f)	99/1
7	p-CH ₃ C)C ₆ H ₄ (4g)	11.5	74 (11g)	25/1
8	PhCH ₂	(4h)	11.5	58 (11h)	99/1
9	$n-C_7H_1$	₅ (4i)	10.5	64 (11i)	99/1
10	<i>n</i> -C ₁₂ H	₂₅ (4j)	8	33 (11j)	64/1

 $^a\,\text{Determined}$ by 300 MHz ^1H NMR spectra of the crude product.





It has been reported that $Hg(OAc)_2$ can react easily with an allene to yield methoxy-mercuration products, i.e., vinylic Hg derivatives Z/E-14 with Z-14 as the major product. The stereoselectivity was determined by the relative stability of the σ -bridged mercurinium ions and

⁽¹⁷⁾ Crystal data for Z-11e: C₉H₈BrIOSe, Mw = 417.92, monoclinic, space group *P*2₁/*c*, Mo Kα, final *R* indices [*I* > 2σ(*I*)] R₁ = 0.0592, wR₂ = 0.1428, *a* = 11.6887(17) Å, *b* = 4.4071(7) Å, *c* = 12.1232(18) Å, *β* = 110.230(2)°, *V* = 585.98(15) Å³, *T* = 20.0 °C, *Z* = 2, reflections collected/ total 3559/unique 2201 (*R*_{int} = 0.1447), no. observation [*I* > 2.00σ(*I*)] 1671, parameters126. CCDC 186926 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

SCHEME 7



the steric hindrance of the incoming methoxy group (Scheme 7). $^{18}\,$

However, even with 1,2-allenyl sulfides **2r** and **2s**, the bromohydroxylation products **10r**-**s** were formed in 35% yield (Z/E = 43:1) and 43% yield (Z/E = 36:1), respectively, indicating that the methyl or butyl group is not playing a critical role in determining the stereoselectivity (Scheme 5). Thus, a rationale for this reaction was shown in Scheme 8. The Z-stereoselectivity for these reactions may be explained by the soft Lewis base–acid interaction between the sulfur or selenium atom and the positively charged X⁺ in Z-**16**.^{19,20} The regioselectivity in these reactions may be controlled by the combined steric and electronic effects of the substituents at the two terminal positions of the allenes.



In conclusion, we have developed a highly regio- and stereoselective addition reaction of 1,2-allenyl sulfides or selenides. Although the real nature controlling the stereoselectivity needs further attention, this reaction provides an efficient route to the isomers of the Z-3organosulfur- or seleno-group-substituted 2-halo-allylic alcohols in a highly stereoselective manner, and it may open up a new area for the control of selectivity in addition reactions of allenes. Further studies in this area are currently being carried out in our laboratory.

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Supporting Information Available: Experimental section, analytical data for compounds not listed in the text, and ¹H NMR and ¹³C NMR spectra of those compounds. Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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