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Stereoselective preparation of (*E*)- and (*Z*)-di- and trisubstituted 1,3-butadienes

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The reaction of γ-(trimethylsilyl)allyltitanocenes, generated by the desulfurizative titanation of trimethylsilyl-substituted allylic sulfides with the titanocene(II)–1-butene complex, with ketones produced β-hydroxy silanes with good to complete *anti*-selectivity. Both (*E*)- and (*Z*)-1,1-disubstituted as well as 1,1,2-trisubstituted 1,3-butadienes are obtained stereoselectively by their Peterson elimination under acidic or basic conditions.

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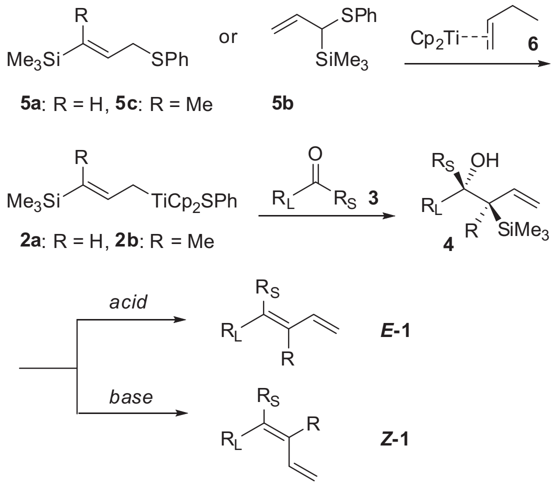
Conjugated dienes are useful synthetic intermediates employed in [4+1],[1] [4+2],[2] [4+3],[3] and other cycloadditions.[2a,4] Therefore their stereoselective preparation has been extensively studied.[5] The major approaches to conjugated dienes include olefination of unsaturated carbonyl compounds,[6] enyne metathesis,[7] and coupling reactions of alkenylmetals with alkenyl (pseudo)halides.[8] Despite the extensive studies described above, an easy access to conjugated dienes with high stereoselectivity still remains a formidable challenge.

We have studied the reactions of ketones with allyltitanocenes generated by the desulfurizative metallation of allylic sulfides with the titanocene(II) reagent. The reaction proceeds with high stereoselectvity[9] or stereospecificity[10] depending on the substitution pattern of allylic sulfides. Encouraged by these results, the diastereoselective addition of silyl group-containing allyltitanocenes was examined for the diversity-oriented synthesis of β,δ-[11] and β,γ-disubstituted[12] *tert*-homoallylic alcohols. Herein we describe the stereoselective and operationally straightforward method for the preparation of both (*E*)- and (*Z*)-di- and trisubstituted conjugated dienes **1** by the reaction of γ-silylallyltitanocenes **2** with ketones **3** and the following Peterson elimination of the resulting β-hydroxy silanes **4** (Scheme 1). Somfai and co-workers reported the preparation of (*E*)-1-monosubstituted 1,3-dienes by the Lewis acid-promoted reaction of 1,3-bis(silyl)propenes with aldehydes.[13] However, the application of this method to the preparation of (*Z*)-1,3-dienes or more highly substituted congeners has not appeared yet.

The reductive titanation of **5a** with titanocene(II)–1-butene complex (**6**) was carried out in THF at 0 °C for 2 h. Subsequent treatment of the resulting organotitanium species with 4-phenyl-2-butenone (**3a**) at −78 °C for 24 h and work-up with 3 M NaOH



Scheme 1. Stereoselective preparation of (*E*)- and (*Z*)-di- and trisubstituted 1,3-butadienes.

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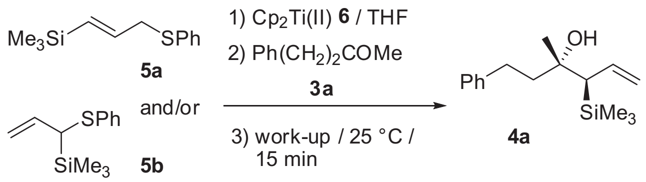
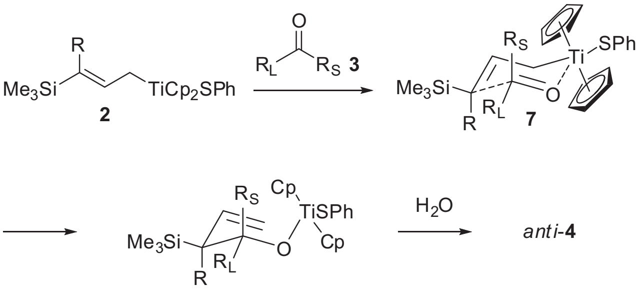
Table 1
Preparation of β-hydroxy silane **4a** under various conditions[a]



Entry	**5a**:**5b**	Work-up	Yield/%[b]	*anti*:*syn*[c]
1	90:10	3 M NaOH	78	86:14
2	90:10	H_2O/THF	78	85:15
3	90:10	pH 10 Buffer/THF	85	85:15
4	90:10	Satd NH_4Cl/THF	89	85:15
5	0:100	pH 10 Buffer/THF	84	85:15
6	47:53	pH 10 Buffer/THF	84	85:15

[a] Conditions: (1) silylallyl sulfide **5** (1.25 equiv), $Cp_2Ti(II)$ **6** (2.5 equiv), 0 °C for 2 h; (2) ketone **3a** (1 equiv), −78 °C for 24 h.
[b] Isolated yield based on **3a** used.
[c] Determined by NMR spectroscopy.

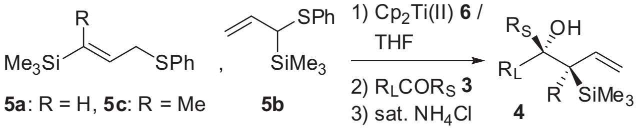


Scheme 2. Stereoselective formation of *anti*-β-hydroxy silanes **4**.

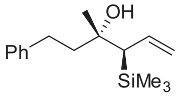
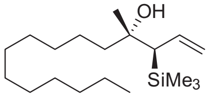
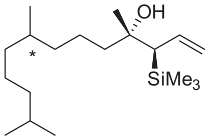
produced the β-hydroxy silane **4a** in 78% yield with 86% diastereoselectivity along with a small amount of the diene **1a** (Table 1, entry 1). The stereochemistry of the major isomer of **4a** was deduced to be *anti* on the basis of the stereochemistry of the diene **1a** produced by the Peterson elimination under the acidic and basic conditions described later. The stereochemical outcome of the reaction suggested that γ-(trimethylsilyl)allyltitanocene with *E*-configuration **2** was stereoselectively produced and it reacted with ketone **3** through the chair-like six-membered transition state **7** in which the larger substituent of **3** occupied the equatorial position (Scheme 2).

To suppress the formation of **1a**, the work-up conditions were examined, and quenching with sat. NH_4Cl aqueous solution resulted in the best yield (entry 4). Since the yield and diastereoselectivity of **4a** are independent of the position of the trimethylsilyl

Table 2
Preparation of β-hydroxy silanes **4**[a]

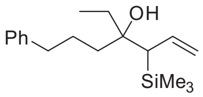
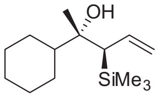
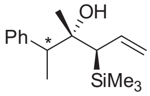
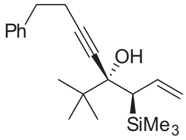
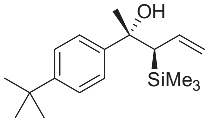
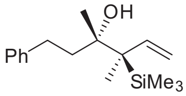
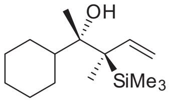
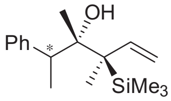


3a: R_L = $Ph(CH_2)_2$; R_S = Me, **3b**: R_L = $Me(CH_2)_{10}$; R_S = Me, **3c**: R_L = $Me_2CH(CH_2)_3CHMe(CH_2)_3$; R_S = Me, **3d**: R_L = $Ph(CH_2)_3$; R_S = Et, **3e**: R_L = *c*-Hex; R_S = Me, **3f**: R_L = $Ph(CH_3)CH$; R_S = Me, **3g**: R_L = *tert*-Bu; R_S = $Ph(CH_2)_2C{\equiv}C$, **3h**: R_L = 4-*tert*-BuC_6H_4; R_S = Me

Entry	**5** (**5a**:**5b**)	**3**		**4** (yield/%[b]; *anti*:*syn*[c])
1	**5a**, **5b** (10:90)	**3a**		**4a** (89; 85:15)
2	**5a**, **5b** (54:46)	**3b**		**4b** (76; 82:18)
3	**5a**, **5b** (24:76)	**3c**		**4c** (80; 82:18)[d]

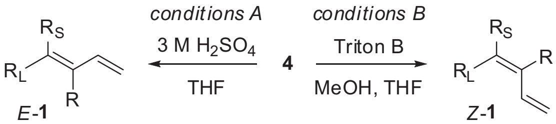
(*continued on next page*)

Table 2 (*continued*)

Entry	**5** (**5a**:**5b**)	**3**	**4** (yield/%[b]; *anti*:*syn*[c])
4[e]	**5a**, **5b** (22:78)	**3d**	 **4d** (70; 58:42)[f]
5	**5a**, **5b** (54:46)	**3e**	 **4e** (80; 100:0)
6[e]	**5a**, **5b** (62:38)	**3f**	 **4f** (82; 100:0)[d]
7	**5a**, **5b** (24:76)	**3g**	 **4g** (58; 100:0)
8[g]	**5a**, **5b** (24:76)	**3h**	 **4h** (75; 100:0)
9[h]	**5c**	**3a**	 **4i** (75; 91:9)
10[h]	**5c**	**3e**	 **4j** (57; 100:0)
11[e,h]	**5c**	**3f**	 **4k** (60; 100:0)[d]

[a] Conditions: (1) silylallyl sulfide **5** (1.25 equiv), $Cp_2Ti(II)$ **6** (2.5 equiv), 0 °C for 2 h; (2) ketone **3** (1 equiv), −78 °C for 18-24 h; 3) 25 °C for 15 min.
[b] Isolated yield based on **3** used.
[c] Determined by NMR spectroscopy.
[d] Configuration of the stereogenic center with asterisk was not necessarily determined.
[e] Quenched with pH 10 buffer.
[f] Ratio of diastereomers, which was determined by GC analysis.
[g] Quenched with MeOH/hexane.
[h] Preparation of **2b** was carried out at −30 °C for 2 h.

Table 3
Preparation of conjugated dienes **1**[a]



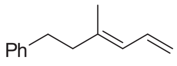
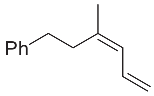
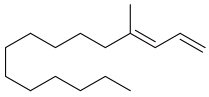
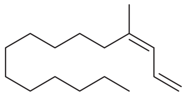
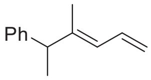
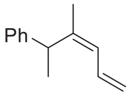
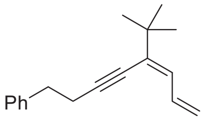
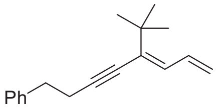
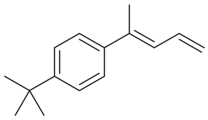
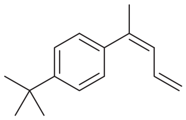
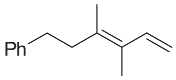
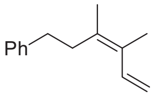
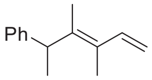
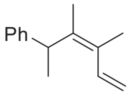
Entry	**4** (*anti*:*syn*)	Conditions	**1** (yield/%[b]; *E*:*Z*[c])
1[d]	**4a** (86:14)	A	 *E*-**1a** (83; 86:14)
2	**4a** (85:15)	B	 *Z*-**1a** (87; 18:82)
3	**4b** (80:20)	A	 *E*-**1b** (80; 83:17)
4	**4b** (79:21)	B	 *Z*-**1b** (96; 21:79)

Table 3 (*continued*)

Entry	**4** (*anti*:*syn*)	Conditions	**1** (yield/%[b]; *E*:*Z*[c])	
5	**4f** (100:0)	A		*E*-**1c** (83; 100:0)
6	**4f** (100:0)	B		*Z*-**1c** (86; 0:100)
7[e]	**4g** (100:0)	A		*Z*-**1d** (80; 0:100)
8	**4g** (100:0)	B		*E*-**1d** (86; 100:0)
9[d,f]	**4h** (100:0)	A		*E*-**1e** (83; 100:0)
10	**4h** (100:0)	B		*Z*-**1e** (91; 0:100)
11	**4i** (87:13)	A		*E*-**1f** (84; 91:9)
12	**4i** (88:12)	B		*Z*-**1f** (92; 12:88)
13	**4k** (100:0)	A		*E*-**1g** (56; 100:0)
14	**4k** (100:0)	B		*Z*-**1g** (89; 0:100)

[a] Conditions A: 3 M H_2SO_4 (3.5 mL/mmol of **4**), 50 °C for 1 h; conditions B: Triton B (40% in MeOH, 4-10 equiv), 25 °C for 1 h.
[b] Isolated yield.
[c] Determined by NMR spectroscopy.
[d] Carried out at 25 °C.
[e] Carried out for 8 h.
[f] Carried out for 0.5 h using $BF_3 \cdot OEt_2$ (4.3 equiv) as an acid catalyst.

group in the allyl phenyl sulfides **5** (see entries 3, 5, and 6), a mixture of **5a** and **5b** was conveniently employed in the following study.

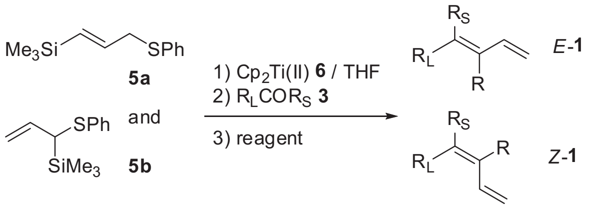
With the optimized reaction conditions in hand, the allylation of a variety of ketones **3** with **5** was examined (Table 2). Similar to the reaction of **3a**, good diastereoselectivity was observed in the reaction of methyl ketones **3b** and **3c** (entries 2 and 3). In contrast, the reaction of ethyl ketone **3d** with allyltitanocene **2a** produced a nearly 1:1 mixture of the diastereomers (entry 4). Only the *anti*-alcohols were produced when the secondary alkyl methyl ketones **3e** and **f** were employed (entries 5 and 6). The *anti*-isomers were also obtained as sole products by the reaction of alkynyl ketone **3g** (entry 7) and aromatic ketone **3h** (entry 8). It is of special note that the homoallylic alcohols bearing two adjacent quaternary carbons were produced with high diastereoselectivity using γ-(trimethylsilyl)crotyl sulfide **5c** (entries 9–11).

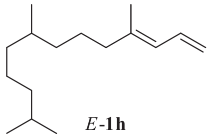
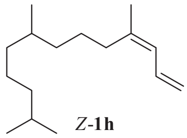
It is well known that the Peterson elimination is a highly stereoselective process. Under acidic conditions, β-hydroxy silanes provide the alkenes by an *anti*-elimination pathway. Conversely, *syn*-elimination proceeds under basic conditions through the formation of pentacoordinate cyclic silicon species.[14] Therefore, it is reasonable to assume that both the (*E*)- and (*Z*)-1,1-disubstituted or -1,1,2-trisubstituted 1,3-butadienes **1** are obtained by the Peterson elimination of β-hydroxy silanes **4**.

Indeed, the treatment of **4a** with 3 M H_2SO_4 in THF at 25 °C for 1 h produced the *E*-diene ***E*-1a** without the loss of stereoisomeric purity (Table 3, entry 1). Under basic conditions using Triton B, in contrast, **4a** was transformed into the (*Z*)-diene ***Z*-1a** with almost the same stereoselectivity (entry 2). These results indicate that the Peterson elimination proceeded with complete stereospecificity. The stereoisomerically pure alcohols **4f**–**h** were transformed into both the (*E*)- and (*Z*)-dienes **1** by similar treatment with acid or base with complete stereoselectivity (entries 5–10).[15] The trisubstituted butadienes **1f** and **g** were also obtained with high stereoselectivity by the treatment of highly substituted β-hydroxy silanes **4i** and **k** (entries 11–14).

To simplify the procedure for the synthesis of dienes **1**, a 'one-pot reaction' was examined in several cases (Table 4). After the reaction of allyltitanocene **2a** with 4-phenyl-2-butanone (**3a**), a methanol solution of Triton B was added to the reaction mixture

Table 4
One-pot transformation of ketones **3** into conjugated dienes **1**[a]



Entry	**5** (**5a**:**5b**)	**3**	Product **1** (reagent)	Yield/%[b]; *E*:*Z*[c]
1	**5a**, **5b** (32:68)	**3a**	*E*-**1a** ($BF_3·OEt_2$[d])	71; 84:16
2	**5a**, **5b** (62:38)	**3a**	*Z*-**1a** (Triton B)	86; 19:81
3	**5a**, **5b** (32:68)	**3b**	*E*-**1b** ($BF_3·OEt_2$)	61; 88:12
4	**5a**, **5b** (66:34)	**3b**	*Z*-**1b** (Triton B)	77; 17:83
5	**5a**, **5b** (67:33)	**3c**	 *E*-**1h** ($BF_3·OEt_2$)	49; 86:14
6	**5a**, **5b** (67:33)	**3c**	 *Z*-**1h** (Triton B)	67; 25:75
7[e]	**5a**, **5b** (32:68)	**3f**	*E*-**1c** ($BF_3·OEt_2$)	63; 100:0
8	**5a**, **5b** (61:39)	**3f**	*Z*-**1c** (Triton B)	83; 0:100

[a] Conditions: (1) silylallyl sulfide **5** (1.25 equiv), $Cp_2Ti(II)$ **6** (2.5 equiv), 0 °C for 2 h; (2) ketone **3** (1 equiv), −78 °C for 18–24 h.; (3) $BF_3·OEt_2$ (8 equiv), 25 °C for 1 h or Triton B (40% in MeOH, 9 equiv), 25 °C for 1 h.

[b] Isolated yield based on **3** used.

[c] Determined by NMR spectroscopy.

[d] $BF_3·OEt_2$ (16 equiv) was used.

[e] Peterson elimination was carried out at reflux for 5 h.

at −78 °C and the mixture was stirred at 25 °C for 1 h to afford the (*Z*)-diene ***Z*-1a** with stereoselectivity comparable to that of the stepwise process (entry 2). Using the same procedure, the (*Z*)-dienes ***Z*-1b**, **c**, and **h** (entries 4, 6, 8) were obtained. By contrast, the one-pot Peterson elimination of β-hydroxy silane **4a** under acidic conditions using H_2SO_4 was unsuccessful and a substantial amount of **4a** remained unchanged. After several attempts, $BF_3·OEt_2$ was found to be the best promoter for the one-pot transformation of **3** to ***E*-1** (entries 1, 3, 5, and 7).

In conclusion, we have established a versatile method for the stereoselective preparation of both (*E*)- and (*Z*)-di- and trisubstituted 1,3-butadienes. These unsaturated compounds are useful motifs for the construction of a variety of cyclic compounds through cycloadditions. Further extension of this method to the preparation of more highly substituted 1,3-butadienes is currently under way.

Supplementary data

Supplementary data (experimental procedures and full characterization of sillyl sulfides and all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.114.

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