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Regio- and stereoselective preparation of highly substituted tertiary homoallylic alcohols

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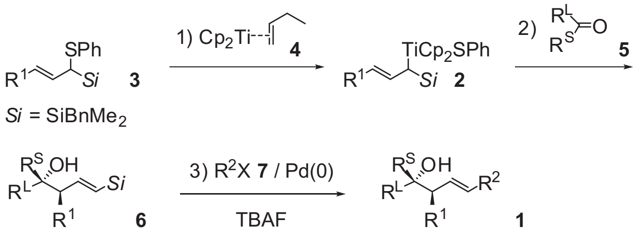
ABSTRACT

The titanocene(II)-promoted reaction of α-(benzyldimethylsilyl)allylic sulfides with ketones proceeded with high regio- and stereoselectivity to give δ-silylhomoallylic alcohols. The following palladium catalyzed cross-couplings with organic halides produced *anti*-(*E*)-β,δ-disubstituted tertiary homoallylic alcohols with complete retention of configuration.

Regio- and stereoselective construction of acyclic systems is a central theme in organic synthesis and efficient new methodologies are still anticipated. Addition of allylmetals to carbonyl compounds has been extensively studied as a useful tool for this purpose.[1] Our recent efforts in this area have been focused on the stereoselective construction of multistereogenic centers including a quaternary center by the reaction of primary allyltitanium species with ketones.[2] Similar steric discrimination of carbonyls based strategy for the construction of adjacent stereocenters has also been examined using allylboron,[3] tin,[4] silicon,[5] and zinc[6] species. An outstanding great challenge in this field is the stereo- and regioselective construction of highly substituted homoallylic alcohol systems and the addition of α,γ-disubstituted allylboranes,[7] stannanes,[8] zirconiums,[9] and samariums[10] to aldehydes which has been applied for this purpose. However, these methods have only been applied to the preparation of β,δ-disubstituted secondary alcohols and preparation of the corresponding tertiary alcohols using these allylmetals has not appeared yet.

Here we report a synthetically straightforward approach for regio-, diastereo-, and stereoselective preparation of β,δ-disubstituted tertiary homoallylic alcohols **1** adjacent to a stereogenic center. The process consists of the titanocene(II)-promoted reaction of α-silylallyltitanocenes **2**, generated by the reductive titanation of readily available α-(benzyldimethylsilyl)allylic sulfides **3** with titanocene(II)-1-butene complex **4**, with ketones **5** and the following cross-coupling between the resulting δ-silylhomoallylic alcohols **6** and organic halides **7** (Scheme 1).

The first step of the synthetic sequence, allylation of carbonyl compounds **5** with α-silylallyltitanocenes **2**, proceeded with perfect regio- and stereoselectivity to produce (*E*)-δ-silylhomoallylic alcohols **6** (Table 1). The diastereoselectivity of the addition of **2** was also excellent. The cinnamyltitanocene **2a** generated from α-(benzyldimethylsilyl)cinnamyl sulfide **3a** reacted with benzaldehyde (**5a**) with complete diastereoselectivity to produce the homoallylic alcohol **6a** (entry 1). The secondary homoallylic alcohols **6b–d** were also obtained in a regio- and stereochemically pure form (entries 2–4). The reactions of **2a** with aromatic and sterically hindered alkyl methyl ketones **5c,d** produced the homoallylic



3a; R^1 = Ph, **3b**; R^1 = Me, **3c**; R^1 = $Ph(CH_2)_2$.
5a; PhCHO, **5b**; $Ph(CH_2)_2CHO$, **5c**; PhCOMe, **5d**; ^{i}PrCOMe,
5e; EtCOMe, **5f**; PhCOEt.

Scheme 1.

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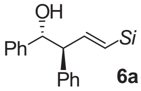
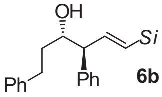
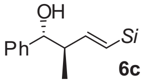
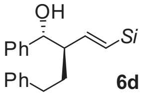
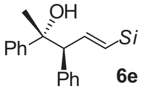
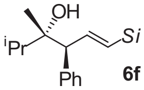
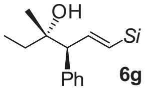
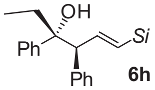
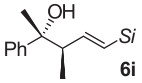
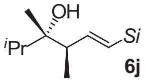
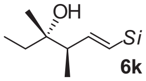
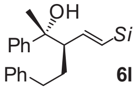
Table 1
Preparation of δ-silylhomoallylic alcohols **6** by the titanocene(II)-promoted reaction of α-silylallylic sulfides **3** with carbonyl compounds **5**[a]

Entry	3	5	Product 6	Yield (%)[b]	*anti*/*syn*[c]
1	**3a**	**5a**	 **6a**	69	100:0
2	**3a**	**5b**	 **6b**	81	93:7
3	**3b**[d]	**5a**	 **6c**	55	90:10
4	**3c**	**5a**	 **6d**	57	96:4[e]
5	**3a**	**5c**	 **6e**	76	>98:2
6	**3a**	**5d**[f]	 **6f**	77	100:0
7	**3a**	**5e**[f]	 **6g**	85	92:8
8	**3a**	**5f**	 **6h**	74	93:7
9	**3b**[d]	**5c**	 **6i**	66	80:20
10	**3b**[d]	**5d**[f]	 **6j**	72	98:2[e]
11	**3b**[d]	**5e**[f]	 **6k**	83	91:9[e]
12	**3c**	**5c**	 **6l**	70	92:8

[a] Conditions: (1) α-silylallyl sulfide **3** (1 equiv), $Cp_2Ti(II)$ **4** (2.0 equiv) in THF at 0 °C for 2 h; (2) carbonyl compound **5** (1.4 equiv) at −40 °C for 24 h.

[b] Isolated yield.

[c] Determinated by NMR analysis.

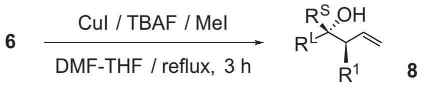
[d] *E*/*Z* = 90:10.

[e] Determined by GC analysis.

[f] 3.0 equiv of the ketone **5** were used.

alcohols **6e**,**f** as sole diastereomers (entries 5 and 6). Even in the case of sterically less crowded methyl ethyl ketone (**5e**), the alcohol **6g** was obtained with high diastereoselectivity (entry 7). Acceptable diastereoselectivity was also obtained in the reaction using propiophenone (**5f**) (entry 8). Although a slight decrease of selectivity was observed, the crotyltitanocene **2b** reacted with ketones to form the tertiary homoallylic alcohols in good yields (entries 9–11). The treatment of γ-aralkyl group substituted allyltitanocene **2c** with **5c** gave the homoallylic alcohol **6l** with high diastereoselectivity (entry 12), suggesting the general synthetic applicability of the reaction.

The stereochemistry of the addition was determined after the protodesilylation of homoallylic alcohols **6** (Scheme 2).[11] Several alcohols **6** were treated with TBAF in the presence of copper(I) iodide and methyl iodide to give the desilylated alcohols **8**.[12] The *anti*-selective formation of homoallylic alcohols **6** was confirmed by comparison with the authentic *anti*-isomers prepared by our method.[2a]



Scheme 2.

To understand the stereochemical pathway, the regio- and stereochemistry of the allyltitanocenes should be considered. In the formation of silyl group substituted organotitanium species, there is a tendency that the compounds in which the silyl group locates at α to the titanium atom become thermodynamically favored. For example, the [2+2]cycloaddition between a 1-trimethylsilylalkyne with a titanium vinylidene complex at room temperature forms a mixture of 2- and 3-trimethylsilyltitanacyclobutenes and refluxing the reaction mixture affords only the 2-trimethylsilyl derivative.[13] This result implies that the α-silyl group substituted organotitanium species are more thermodynamically stable than other possible regioisomers. On the basis of the above assumption, the observed regio- and stereoselectivity of the reaction is explained by the selective formation of α-silylallyltitanocenes **2** with *E*-configuration and their addition to carbonyl compounds **5** via the well established chair-like six-membered transition states **Ts** in which the larger group of carbonyls occupies an equatorial position (Scheme 3). The *E* configuration of δ-silylhomoallylic alcohols **6** indicates that the reaction proceeds via the transition state **Ts-1**, in which the equatorial benzyldimethylsilyl group suffers only gauche-like interactions with two Cp rings. In contrast, another possible transition state **Ts-2** is destabilized by the gauche-like interaction between the axial silyl group and the Cp ring and the 1,3-alyllic strain of allylsilane moiety.

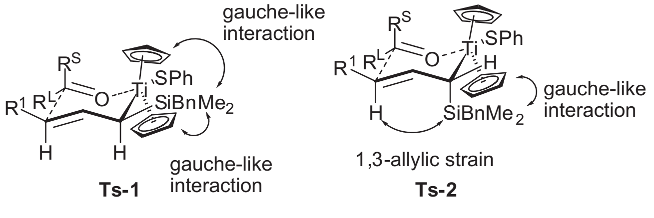
The δ-silylhomoallylic alcohols **6** thus obtained were readily transformed into β,δ-disubstituted homoallylic alcohols **1** by the palladium-catalyzed cross-coupling with aryl, alkenyl, benzyl, and methyl halides **7** (Scheme 4).[14] All the reactions proceeded with complete retention of configuration in good yields (Table 2).

In conclusion, it should be noted that the titanocene(II)-promoted allylation of ketones with α-silylallylic sulfides and the following palladium(0)-catalyzed cross-coupling with organic halides constitute a convenient way for the regio-, stereo-, and diastereoselective synthesis of highly substituted tertiary homoallylic alcohols. The present approach enjoys an advantage that a variety of homoallylic alcohols bearing four different substituents at α, β, and δ-positions, each of which originated from ketones, allylic sulfides, and organic halides, are readily accessible. Further study on the transformation of δ-silylhomoallylic alcohols is now under investigation.

Typical experimental procedure for preparation of *anti*-homoallylic alcohols 1

To a THF (12 mL) suspension of Cp_2TiCl_2 (996 mg, 4.0 mmol) was added a hexane solution of BuLi (1.65 M, 4.8 mL, 8.0 mmol) at −78 °C under argon. After 1 h, a THF (8 mL) solution of **3a** (749 mg, 2.0 mmol) was added dropwise over 5 min to the reaction mixture. The mixture was warmed up to 0 °C and stirred for 2 h. After stirring the mixture at −40 °C for 15 min, a THF (4 mL) solution of methyl ethyl ketone (**5e**) (432 mg, 6.0 mmol) was added and the mixture was further stirred for 24 h. The reaction was quenched by addition of a mixture of 1 M NaOH (5 mL) and THF (5 mL), and the insoluble materials were filtered off through Celite and washed with ether. The organic materials were extracted with ether and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (hexane/AcOEt = 9:1, v/v) to give 6-(benzyldimethylsilyl)-3-methyl-4-phenyl-5-hexen-3-ol (**6g**) (578 mg, 85%).

Pd_2dba_3 (9 mg, 0.01 mmol) was added to a THF (1.2 mL) solution of **6g** (68 mg, 0.2 mmol) at 25 °C and then a THF solution of TBAF (1 M, 0.44 mL, 0.44 mmol) was added dropwise to the reaction mixture. A THF (0.8 mL) solution of 4-iodoanisole (**7a**) (47 mg, 0.2 mmol) was added and the mixture was stirred for 3 h. The reaction was quenched by addition of water and the insoluble materials were filtrated off through Celite. The organic materials were extracted with Et_2O and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by PTLC (hexane/AcOEt = 9:1, v/v) to give 3-methyl-6-(4-methoxyphenyl)-4-phenyl-5-hexene-3-ol (**1a**) (46 mg, 78%).



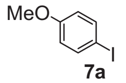
Scheme 3.

$$\mathbf{6} \xrightarrow[\text{Pd}_2\text{dba}_3\text{ / TBAF / THF}]{\text{R}^2\text{X }\mathbf{7}} \mathbf{1}$$

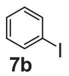
Scheme 4.

Table 2
Pd-catalyzed cross-coupling of δ-silylhomoallylic alcohols **6**[a]

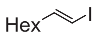
Entry	6	7	1	Yield (%)[b]	*anti:syn*[c]
1	**6g**	**7a**	**1a**	78	91:9
2	**6k**	**7a**	**1b**	85	91:9
3	**6k**	**7b**	**1c**	82	93:7
4	**6g**	**7c**	**1d**	50	89:11
5	**6k**	**7c**	**1e**	52	89:11[d]
6	**6g**	**7d**	**1f**	63	91:9
7	**6g**	**7e**	**1g**	75	90:10
8	**6k**	**7e**	**1h**	81	89:11



7a



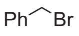
7b



7c

Me-I

7d



7e

[a] Condition: (3) homoallylic alcohol **6** (1 equiv), halide **7** (1 equiv), Pd_2dba_3 (5 mol %), TBAF (2.2 equiv) in THF at 25 °C for 3 h.

[b] Isolated yield.

[c] Determinated by NMR analysis.

[d] Determined by GC analysis.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.111.

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11. Diastereoselectivity of the secondary alcohols **6a**–**d** was determined on the basis of the coupling constant between α and β methine protons (see Supplementary data).
12. Compound **8a**; $R^L = {}^iPr$, $R^S = Me$, R = Ph, 68%, *anti*/*syn* = 100:0: **8b**; $R^L = Et$, $R^S = Me$, R = Ph, 71%, *anti*/*syn* = 92:8: **8c**; $R^L = Ph$, $R^S = Me$, R = Me, 83%, *anti*/*syn* = 78:22: **8d**; $R^L = Ph$, $R^S = Me$, R = $PhCH_2CH_2$, 49%, *anti*/*syn* = 94:6. Trost and co-workers reported the copper(I) iodide–TBAF promoted desilylation of alkenyltriethoxysilanes. The desilylation of **6g**, however, produced **8b** only in 38% yield under the similar conditions without methyl iodide. Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922.
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