Organic Letters
Letter
pubs.acs.org/OrgLett

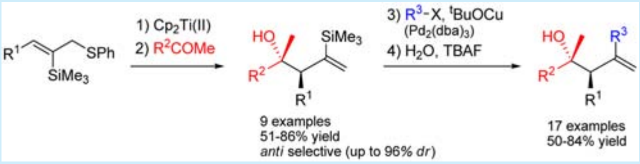
Diversity-Oriented Stereoselective Synthesis of β,γ-Disubstituted *tert*-Homoallylic Alcohols

Takeshi Takeda,* Sota Amarume, Ippei Sekioka, and Akira Tsubouchi

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

Supporting Information

ABSTRACT: The successive treatment of β-(trimethylsilyl)-allyl phenyl sulfides with titanocene(II)-1-butene complex and ketones produced tertiary γ-(trimethylsilyl)homoallylic alcohols with good *anti*-selectivity, which reacted with a variety of organic halides in the presence of copper(I) *tert*-butoxide to afford the cross-coupling products, γ-substituted homoallylic alcohols.

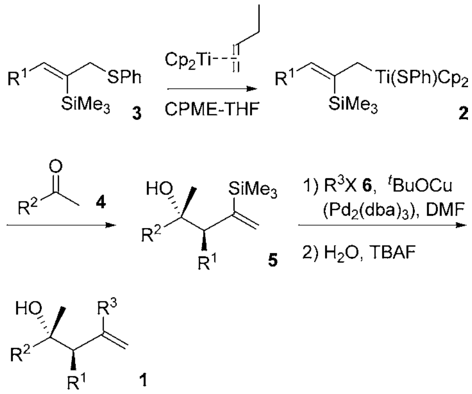


Diastereoselective allylation of carbonyl compounds with allylmetal species is a useful process for the stereoselective construction of acyclic systems and frequently employed for the synthesis of natural products.[1] The application of this process, however, sometimes encounters obstacles such as appropriate organometallic reagents are not easily available.

Recently, we have disclosed the highly diastereoselective preparation of *tert*-homoallylic alcohols bearing two or three stereogenic centers by the addition of allyltitanocenes to ketones.[2] The γ-substituted *E*-allyltitanocenes are readily prepared by the desulfurizative titanation of α- or γ-monosubstituted allylic sulfides with titanocene(II)-1-butene complex with complete stereo- and regioselectivity.[2a] While the addition of allylmetals to ketones generally exhibits rather limited diastereoselectivity compared with their addition to aldehydes, the organotitanium species thus formed react with ketones to produce *tert*-homoallylic alcohols with unexpectedly high *anti*-selectivity. Aside from the chemistry of allyltitanocenes, we have continuously studied the preparation of alkenyl and arylcopper(I) species by the silicon migration of silyl-group-containing copper(I) alkoxides[3] or copper(I) enolates.[4] The organocopper(I) species thus formed are highly reactive toward organic halides, including allylic, benzylic, and alkyl halides.

All these results of organotitanium and silicon chemistry prompted us to investigate the highly diastereoselective preparation of γ-substituted homoallylic alcohols **1**. The process consists of the reaction of β-(trimethylsilyl)allyltitanium reagents **2**, generated by the reductive titanation of β-(trimethylsilyl)allyl phenyl sulfides **3**, with ketones **4** and the copper(I) *tert*-butoxide-promoted reaction of the resulting γ-(trimethylsilyl)homoallylic alcohols **5** with organic halides **6** (Scheme 1). This process enables us to prepare *tert*-homoallylic alcohols bearing a variety of substituents at the β-position from the same starting materials. The similar diversity-oriented synthesis of δ-substituted homoallylic alcohols by the titanoene(II)-promoted reaction of α-(benzyldimethylsilyl)allyl phenyl sulfides with ketones and the following cross-coupling with organic halides has been reported by us.[5]

Scheme 1. Diversity-Oriented Synthesis of γ-Substituted Homoallylic Alcohols

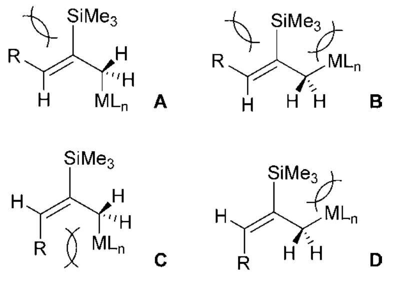


The treatment of β-(trimethylsilyl)crotyl phenyl sulfide **3a** with a titanocene(II)-1-butene complex in cyclopentyl methyl ether (CPME)−THF at 0 °C for 2 h generated the allyltitanium species **2**, which then reacted with acetophenone **4a** at −40 °C for 18 h to produce the γ-(trimethylsilyl)homoallylic alcohol **5a** with 90% *anti* selectivity in 69% yield.[6] The result indicates that the desulfurizative titanation of **3a** generated the *Z*-allyltitanium species **2a**, which reacted with **4a** through the well-established six-membered chairlike transition state. Knochel and co-workers reported the stereoselective formation of *syn*-**5a** by the zinc promoted reaction of β-(trimethylsilyl)crotyl chloride with **4a** through the formation of an *E*-allylzinc reagent.[7] It is of great interest that the stereochemical outcome of our reaction is completely different from that of their reaction.

Received: January 9, 2015
Published: February 17, 2015

We believe that the difference between the stereochemical courses of two reactions could be explained by the difference in bulkiness between the divalent zinc and tetravalent titanium. To rationalize the stereoselective formation of *Z*-allyltitanocenes, the two major conformations for both the *Z*- and *E*-allylmetals bearing a trimethylsilyl group at the *β*-position should be considered (Scheme 2). The stereoselective formation of *Z*-allylzinc species is assumed to be attributable to the unfavorable steric interaction between the *γ*-substituent and the *β*-silyl group in the conformations **A** and **B**. Due to the sterically less bulky zinc moiety, the 1,3-allylic strain between the *γ*-substituent and the zinc moiety in conformation **C** and the steric constraint between the silyl group and the zinc moiety in conformation **D** are negligible, and hence the *E*-allylzinc reagent is relatively more stable than its *Z*-isomer. In the case of the formation of allyltitanocene **1**, in contrast, the repulsions between the sterically demanding titanocene moiety and other groups in the conformations other than **A** are more serious than the strain caused by the crowding of the *γ*- and the *β*-substituents in conformation **A**. As a result, the *Z*-allyltitanocene is preferentially produced.

Scheme 2. Major Conformations of Allyltitanocenes 1



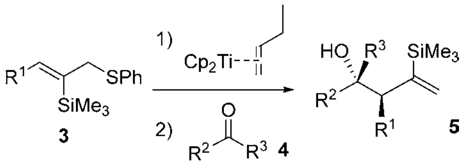
M = Ti, Zn

Under the same reaction conditions, the allylation of several carbonyl compounds **4** with *β*-(trimethylsilyl)allyl sulfides **3** was performed and a variety of *γ*-silyl homoallylic alcohols **5** were obtained with *anti*-selectivity (Table 1). The diastereoselectivity was high enough even when the sterically less demanding ketones, such as ethyl methyl ketone **4c**, were employed (entry 7). The reaction using benzaldehyde **4d** also gave the *anti*-secondary homoallylic alcohol **5h** with high diastereoselectivity (entry 8).

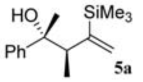
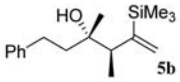
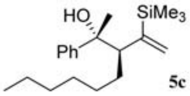
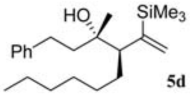
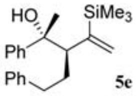
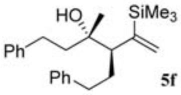
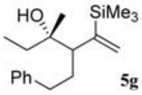
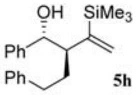
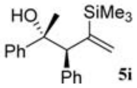
The key step of the previously reported copper(I)-mediated cross-couplings is the transmetalation of pentacoordinated silicates with copper(I) salt to form organocopper species. Indeed the reaction of the fluoride ion coordinated, pentacoordinated silicates, generated by the treatment of alkenylbenzyldimethylsilanes with tetrabutylammonium fluoride, with copper(I) iodide produced alkenylcopper(I) species.[5b] The geometry of *γ*-silyl alcohols **5** would allow the formation of five-membered pentacoordinated cyclic silicates **7** (Scheme 3). Therefore, the treatment of these alcohols **5** with copper(I) *tert*-butoxide is expected to afford the alkenylcopper(I) species **8** through the Si−C bond cleavage. The organometallic compounds **8** thus formed would then react with organic halides **6** to produce the cross-coupling products **1**.

In keeping with this notion, the homoallylic alcohol **5a** was successively treated with copper(I) *tert*-butoxide and allyl chloride **6a** in DMF at 0 °C for 1 h and then at 25 °C for 18 h

Table 1. Preparation of *γ*-Silyl Homoallylic Alcohols 5[a]

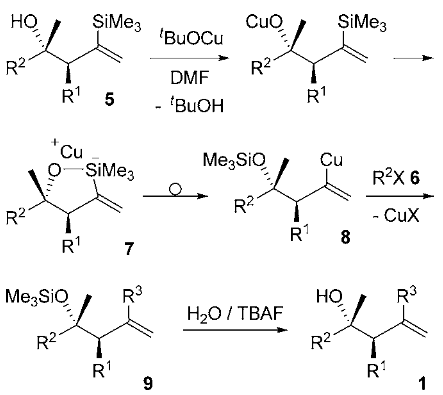


3a: R^1 = Me, **3b**: R^1 = Hex, **3c**: R^1 = Ph$(CH_2)_2$
3d: R^1 = Ph
4a: R^2 = Ph; R^3 = Me, **4b**: R^2 = Ph$(CH_2)_2$; R^3 = Me
4c: R^2 = Et; R^3 = Me, **4d**: R^2 = Ph; R^3 = H

entry	3	4	5	yield, %[b] (dr)[c]
1	**3a**	**4a**	 **5a**	69 (90:10)
2	**3a**	**4b**	 **5b**	75 (80:20)
3	**3b**	**4a**	 **5c**	82 (95:5)
4	**3b**	**4b**	 **5d**	86 (85:15)
5	**3c**	**4a**	 **5e**	78 (96:4)
6	**3c**	**4b**	 **5f**	73 (83:17)
7	**3c**	**4c**	 **5g**	58 (86:14)
8	**3c**	**4d**	 **5h**	59 (91:9)
9	**3d**	**4a**	 **5i**	51 (84:16)

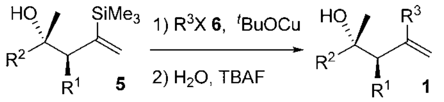
[a] Conditions: (1) *β*-silylallyl sulfide **3** (1.25 equiv), $Cp_2Ti(II)$ (2.5 equiv), 0 °C for 2 h; (2) ketone **4** (1 equiv), −40 °C for 18 h. [b] Isolated yield based on ketone **4** used. [c] Determined by NMR analysis.

Scheme 3. Copper(I)-promoted Cross-coupling of *γ*-Silyl Homoallylic Alcohols 5

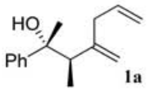
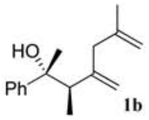
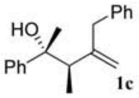
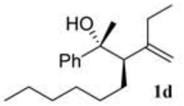
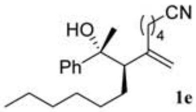
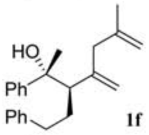
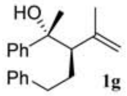
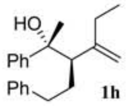
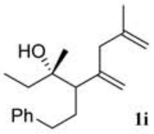
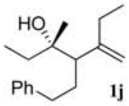
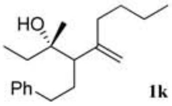


to produce the trimethylsilyl ether **9a**. The γ-substituted homoallylic alcohol **1a** was obtained in 84% yield by the hydrolysis of crude silyl ether **9a** with water/tetrabutylammonium fluoride (TBAF) (entry 1, Table 2). The similar allylation also took place using methallyl chloride **6b** (entries 2, 6, and 9).

Table 2. Cross-Coupling of γ-(Trimethylsilyl)homoallylic Alcohols 5 with Allyl, Benzyl, and Alkyl Halides[a]



6a; CH_2=$CHCH_2Cl$, **6b**; CH_2=$CMeCH_2Cl$, **6c**; $PhCH_2Br$
6d; MeI, **6e**; EtI, **6f**; BuI, **6g**; $NC(CH_2)_4I$

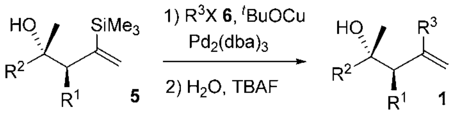
entry	5 (dr)	6	1	yield, %[b] (dr)[c]
1	**5a** (89:11)	**6a**	 **1a**	84 (85:15)
2	**5a** (90:10)	**6b**	 **1b**	71 (91:9)
3	**5a** (90:10)	**6c**	 **1c**	80 (90:10)
4	**5c** (96:4)	**6e**	 **1d**	78 (96:4)
5	**5c** (96:4)	**6g**	 **1e**	58 (98:2)
6	**5e** (94:6)	**6b**	 **1f**	72 (95:5)
7	**5e** (94:6)	**6d**	 **1g**	79 (96:4)
8	**5e** (95:5)	**6e**	 **1h**	80 (96:4)
9	**5g** (100:0)	**6b**	 **1i**	76 (100:0)
10	**5g** (100:0)	**6e**	 **1j**	75 (100:0)
11	**5g** (100:0)	**6f**	 **1k**	62 (100:0)

[a] Conditions: (1) homoallylic alcohol **5** (1 equiv), organic halide **6** (3 equiv), ^{t}BuOCu (3 equiv), 0 °C for 1 h then 25 °C for 18 h; (2) TBAF (3 equiv), 25 °C for 15 h. [b] Isolated yield based on the alcohol **5** used. [c] Determined by NMR analysis.

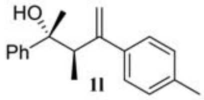
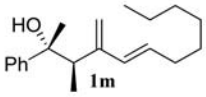
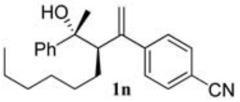
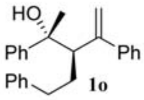
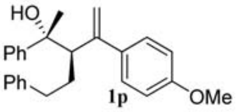
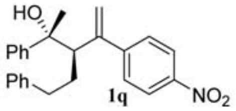
Benzyl bromide and methyl iodide were also reactive toward the organocopper intermediates (entries 3 and 7). It is of special note that the reaction using alkyl halides having a β-hydrogen such as ethyl iodide (entries 4, 8, and 10), butyl iodide (entry 11), and even the alkyl iodide bearing an acidic hydrogen (entry 5) produced the cross-coupling products in good yields. In all these reactions, the configuration of homoallylic alcohols was virtually completely retained.

It is expected that the transmetalation of putative alkenylcopper intermediates with haloorganopalladium(II) species, generated by the oxidative addition of C(sp^2)−X electrophiles to palladium(0), results in the formation of diorganopalladiums, which then afford cross-coupling products through the reductive elimination process. Indeed, the copper(I) *tert*-butoxide-promoted reaction of homoallylic alcohol **5d** with iodotoluene **6h** in the presence of tris(dibenzylideneacetone)dipalladium(0) produced the arylation product **1o** in 76% yield with complete retention of configuration (Table 3, entry 4). The cross-coupling of **5** took place with both electron-rich (entries 1 and 5) and electron-deficient (entries 3 and 6) aryl halides. Notably, alkenyl halides could be employed as coupling partners (see

Table 3. Cross-Coupling of γ-(Trimethylsilyl)homoallylic Alcohols 5 with Aryl and Alkenyl Halides[a]



6h; PhI, **6i**; 4-MeC_6H_4I, **6j**; 4-$MeOC_6H_4I$, **6k**; 4-NCC_6H_4I
6l; 4-$O_2NC_6H_4I$, **6m**; (*E*)-HexCH=CHI

entry	5 (dr)	6	1	yield, %[b] (dr)[c]
1	**5a** (88:12)	**6i**	 **1l**	69 (86:14)
2	**5a** (90:10)	**6m**	 **1m**	63 (95:5)
3	**5c** (96:4)	**6k**	 **1n**	68 (96:4)
4	**5e** (96:4)	**6h**	 **1o**	76 (96:4)
5	**5e** (97:3)	**6j**	 **1p**	69 (100:0)
6	**5e** (95:5)	**6l**	 **1q**	50 (96:4)

[a] Conditions: (1) homoallylic alcohol **5** (1 equiv), organic halide **6** (3 equiv), ^{t}BuOCu (3 equiv), $Pd_2(dba)_3$ (15 mol %), 0 °C for 1 h then 25 °C for 18 h; (2) TBAF (3 equiv), 25 °C for 15 h. [b] Isolated yield based on the alcohol **5** used. [c] Determined by NMR analysis.

entry 2). The double bond geometry of alkenyl halides was also completely retained during the cross-coupling event.

In conclusion, we have developed a diversity-oriented strategy for the construction of γ-substituted *anti*-homoallylic alcohols which consists of the addition of silyl-group-containing allyltitanocenes to ketones and the copper(I)-mediated cross-coupling of the resulting γ-silyl homoallylic alcohols. In sharp contrast with the Hiyama-type cross-couplings, which generally require the use of rather difficult to handle heteroatom-functionalized organosilanes,[8] the trimethylsilyl group of the bench-stable γ-silyl homoallylic alcohols can be displaced with a variety of alkyl, allyl, aryl, and alkenyl groups.

Further study on the diversity-oriented strategy for the construction of unsaturated systems using silyl-group-containing organotitanium species is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full characterization of all compounds. This material is available free of charge via Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: takeda-t@cc.tuat.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number 26410037.

■ REFERENCES

(1) For a recent review, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595.

(2) (a) Yatsumonji, Y.; Nishimura, T.; Tsubouchi, A.; Noguchi, K.; Takeda, T. *Chem.—Eur. J.* **2009**, *15*, 2680. (b) Takeda, T.; Nishimura, T.; Yatsumonji, Y.; Noguchi, K.; Tsubouchi, A. *Chem.—Eur. J.* **2010**, *16*, 4729. (c) Takeda, T.; Nishimura, T.; Yoshida, S.; Saiki, F.; Tajima, Y.; Tsubouchi, A. *Org. Lett.* **2012**, *14*, 2042. (d) Takeda, T.; Yoshida, S.; Nishimura, T.; Tsubouchi, A. *Tetrahedron Lett.* **2012**, *53*, 3930. (e) Takeda, T.; Yamamoto, M.; Yoshida, S.; Tsubouchi, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7263.

(3) (a) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811. (b) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450. (c) Taguchi, H.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2003**, *44*, 5205. (d) Taguchi, H.; Takami, K.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2004**, *45*, 429. (e) Tsubouchi, A.; Itoh, M.; Onishi, K.; Takeda, T. *Synthesis* **2004**, 1504. (f) Tsubouchi, A.; Muramatsu, D.; Takeda, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12719. (g) Takeda, T.; Obata, R.; Muramatsu, D.; Takeda, Y.; Tsubouchi, A. *Chem. Commun.* **2014**, *50*, 15156.

(4) (a) Taguchi, H.; Miyashita, H.; Tsubouchi, A.; Takeda, T. *Chem. Commun.* **2002**, 2218. (b) Tsubouchi, A.; Onishi, K.; Takeda, T. *J. Am. Chem. Soc.* **2006**, *128*, 14268. (c) Tsubouchi, A.; Matsuda, H.; Kira, T.; Takeda, T. *Chem. Lett.* **2009**, *38*, 1180. (d) Tsubouchi, A.; Enatsu, S.; Kanno, R.; Takeda, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7089. (e) Tsubouchi, A.; Sasaki, N.; Enatsu, S.; Takeda, T. *Tetrahedron Lett.* **2013**, *54*, 1264.

(5) (a) Takeda, T.; Wasa, H.; Tsubouchi, A. *Tetrahedron Lett.* **2011**, *52*, 4575. (b) Takeda, T.; Matsumura, R.; Wasa, H.; Tsubouchi, A. *Asian J. Org. Chem.* **2014**, *3*, 838. The diversity oriented synthesis of conjugated dienes and related compounds by the combination of a benzyldimethylsilyl group containing titanium carbene complexes with carbonyl compounds and alkynes and the following copper(I)-promoted cross-coupling of the resulting alkenylbenzyldimethylsilanes with organic halides was also reported; (c) Takeda, T.; Mori, A.; Fujii, T.; Tsubouchi, A. *Tetrahedron* **2014**, *70*, 5776.

(6) The *anti*-stereochemistry of **5a** was confirmed by comparison with the reported NMR data.[7] The stereochemistry of **5b** and **5i** was also assigned by comparison with the NMR data of authentic homoallylic alcohols[2a] after the protodesilylation by the treatment with NaH (2.1 equiv) in HMPA−THF at 25 °C for 18 h.[7]

(7) Helm, M. D.; Mayer, P.; Knochel, P. *Chem. Commun.* **2008**, 1916.

(8) For selected reviews, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chicheter, 2004; p 338. (b) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 163. (c) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (d) Chang, W.-T. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. *Org. React.* **2011**, *75*, 213. (e) Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 1845. For recent examples, see: (f) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004. (g) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (h) Molander, G. A.; Iannazzo, L. *J. Org. Chem.* **2011**, *76*, 9182. (i) Monguchi, Y.; Yanase, T.; Mori, S.; Sajiki, H. *Synthesis* **2013**, *45*, 40.