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A Novel Synthesis of Functionalized Allylsilanes†

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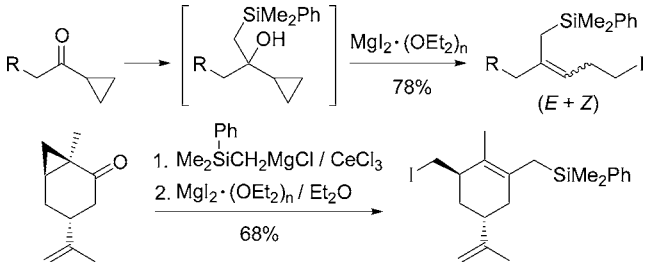
ABSTRACT



A novel facile synthesis of substituted and functionalized allylsilane has been developed. This essentially one-pot procedure involves (1) (dimethylphenylsilyl)methyl cerium chloride addition to cyclopropyl ketone and (2) MgI_2 etherate-mediated Julia homoallylic transposition of the corresponding cyclopropyl carbinol. The bifunctional homoiodo allylsilanes, readily accessible by this method, would be useful and versatile synthons in organic synthesis.

Allylsilanes are valuable and extremely versatile intermediates in synthetic organic chemistry for a variety of stereocontrolled C−C bond formation, carbocyclic ring-forming reactions.[1] Numerous methods have thus been developed for the synthesis of allylsilanes of various types.[2] In connection with an ongoing project on the total synthesis of Labdane diterpenoids based on a well-established general biomimetic polyene cationic cyclization strategy (Figure 1),[3] we disclose here a novel and efficient synthetic method for the synthesis of highly substituted and functionalized allylsilanes such as epoxy allylsilane **1**, the projected biomimetic cyclization precursor.

In an attempt to utilize the Julia homoallylic transposition protocol (Julia olefination synthesis)[4] for the synthesis of a trisubstituted allylsilane model compound **5**, we devised a synthetic plan as shown in Scheme 1, beginning with cyclopropyl carbinol **3**, which was prepared from homogeranyl cyclopropyl ketone **2**[5] by carbonyl addition of a (trimethylsilyl)methyl cerium reagent derived from the

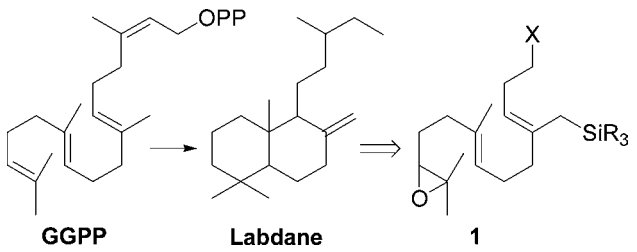


Figure 1. Biomimetic strategy for Labdane diterpenoids.

† Dedicated to Prof. Marc Julia.

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(1) For a review, see: Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(2) For a review on allylsilanes, see: Sarkar, T. K. In *Science of Synthesis: Houben−Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: 2002, New York; Vol. 4, pp 837−962. See also: Sarkar, T. K. *Synthesis* **1990**, 969 and 1101.

(3) For general reviews, see: (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513. (c) Coates, R. M.; Conradi, R. A.; Ley, D. A.; Akeson, A.; Harada, J.; Lee, S.-C.; West, C. A. *J. Am. Chem. Soc.* **1976**, *98*, 4659. For recent examples, see: (d) Ravn, M. M.; Coates, R. M.; Flory, J. E.; Peters, R. J.; Croteau, R. *Org. Lett.* **2000**, *2*, 573. (e) Aggarwal, V. K.; Bethel, P. A.; Giles, R. *Chem. Commun.* **1999**, 325. (f) Kashibuchi, Y.; Fukumoto, T.; Oguchi, M.; Hirukawa, T.; Kato, T. *Heterocycles* **1998**, *49*, 255. (g) Coates, R. M.; Yee, N. K. N. *J. Org. Chem.* **1992**, *57*, 4598. (h) Jognson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852.

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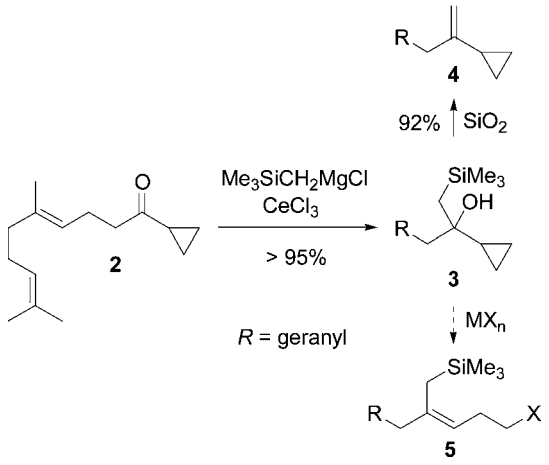
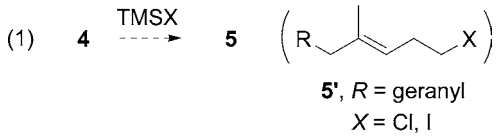
Scheme 1

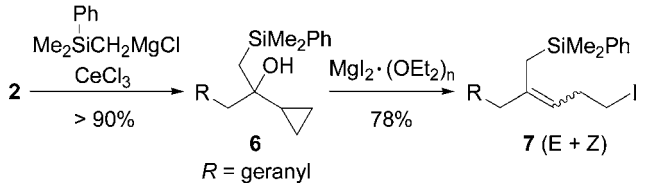


corresponding magnesium chloride reagent and anhydrous $CeCl_3$. However, the labile keto adduct **3** underwent rapid Peterson-type elimination[6] upon exposure to silica gel to give cyclopropyl alkene **4** exclusively during the attempted chromatographic purification. Although the crude carbonyl adduct **3** is relatively stable for structural characterization (spectroscopic), all efforts[4] for the Julia-type olefination by nucleophilic ring-opening of cyclopropane leading to the expected trimethylallylsilane **5** resulted solely in the formation of elimination product **4** instead.



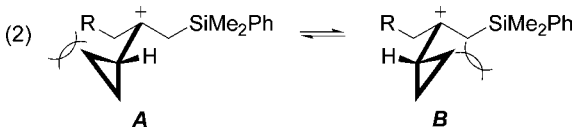
Attempted conversion of cyclopropyl alkene **4** to **5** by the action of trimethylsilyl halides (TMSX, X = Cl, I) also failed by affording homoallylic halides **5′** (X = Cl, I) as the major isolable (*E*)-isomeric product (eq 2), via presumably a protic acid-mediated Julia-type process. In hoping that the sterically more bulky silyl substituents might diminish the competitive Peterson elimination pathway and provide us a chance to effect the designated Julia homoallylic transposition, the cyclopropyl keto adduct **6** was prepared analogously from the (dimethylphenylsilyl)methyl cerium reagent in good yield, which is indeed more stable than the corresponding adduct **3**, as evidenced by ready chromatographic purification on silica gel (Scheme 2). Employing various metal halides

Scheme 2



as a Lewis acidic mediator[4e,f] allowed the Julia ring-opening homoallylation of **6** to be examined.

After considerable experimentation, we were delighted to find that treatment of **6** with MgI_2 etherate[7] in diethyl ether furnished the desired Julia-type ring-opening product **7** in 78% yield as a mixture of (*E*,*Z*)-isomers (ca. 1:1), without significant formation (<5%) of Peterson elimination product **4** (Scheme 2). Although commercially available powdered MgI_2 could also be used for this reaction, the reaction is found to be slower and contaminated by a significant amount of elimination product **4**. Other metal halides, i.e., LiX, ZnX_2 (X = Cl, Br, I), or $MgBr_2$, all led to rapid production of elimination product **4**. It is especially worth noting that the MgI_2 etherate is uniquely effective for the homoallylic transposition of (dimethylphenylsilyl)methyl cyclopropyl carbinol **6**.



We reasoned that the following factors might account for the success of this substrate−reagent combination: (1) the steric bulkiness[8] of dimethylphenylsilyl grouping deters the attack of anionic nucleophile (here an iodo anion) on the silicon center, thus diminishing the Peterson elimination (path *a*); (2) the enhanced β-effect of silicon[8] due to the more electron-rich phenyl substituent, leading to a more stable cationic intermediate **i** (Scheme 3), which might facilitate the nucleophilic ring-opening of the cyclopropane by iodo anion attack of a pseudo S_N2' type (path *b*); and (3) the softness of the more dissociated iodo anion of the mild Lewis acid MgI_2 etherate tends to favor the nucleophilic attack on the carbon atom (sp^2 character) of the cyclopropane ring (Julia-type ring-opening pathway). The delicate reactivity alternation demonstrated here again the uniqueness of the MgI_2 etherate as a mild Lewis acid as well as effective source of iodide ion as a cyclopropane ring-opening nucleophile.[4e,f] The twist of the usually facile Peterson elimination pathway

(4) For earlier seminal works, see: (a) Julia, M.; Julia, S.; Guégan, R.; *Bull. Soc. Chim. Fr.* **1960**, 1072. (b) Julia, M.; Julia, S.; Tchen, S.-Y.; Neuville, C. *Bull. Soc. Chim. Fr.* **1960**, 1381. (c) Julia, M.; Julia, S.; Du Chaffaut, J. M. *Bull. Soc. Chim. Fr.* **1960**, 1735. (d) Julia, M.; Julia, S.; Tchen, S.-Y. *Bull. Soc. Chim. Fr.* **1961**, 1849. For later modifications, see: (e) Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882. (f) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566.

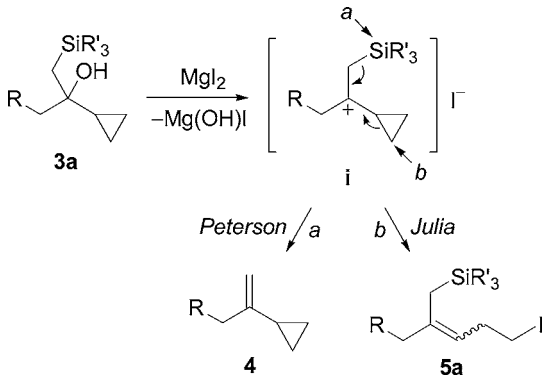
(5) Prepared from geranyl iodide by alkylation with cyclopropyl methyl ketone (LDA, −78 °C, THF) in 52% yield.

(6) For a review on β-silyl alcohols and the Peterson reaction, see: Ager, D. J. In *Science of Synthesis: Houben−Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: 2002, New York; Vol. 4, pp 789−809.

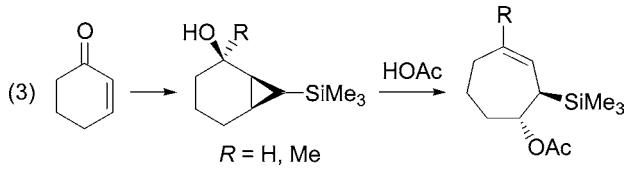
(7) Magnesium(II) iodide and its etherate have emerged as unique Lewis acidic catalysts in a number of synthetic transformations and organic reaction catalysis; for recent examples, see: (a) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (b) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (c) Li, W.-D. Z.; Zhang, X.-X. *Org. Lett.* **2002**, *4*, 3485 and references therein.

(8) We are currently investigating these factors by incorporating other trisubstituted silyl groupings in β-silyl cyclopropyl carbinol adducts, for example, triisopropylsilyl, triethylsilyl (as suggested by a reviewer), and (*para*-methoxyphenyl)dimethylsilyl, etc.

Scheme 3

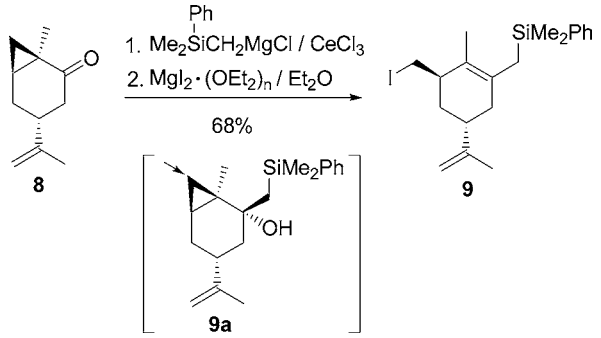


of β-silyl cyclopropyl carbinol of type **6** toward the Julia homoallylic transposition is a result of the synergetic effect of bulky and electron-rich silyl substituent and the strained, yet cation-stablizing cyclopropane ring system. The lower stereoselectivity (*E* vs *Z*) may be attributed to the relatively even steric interaction of two conformers (**A** and **B**, eq 2) of the cationic intermediate **i**.



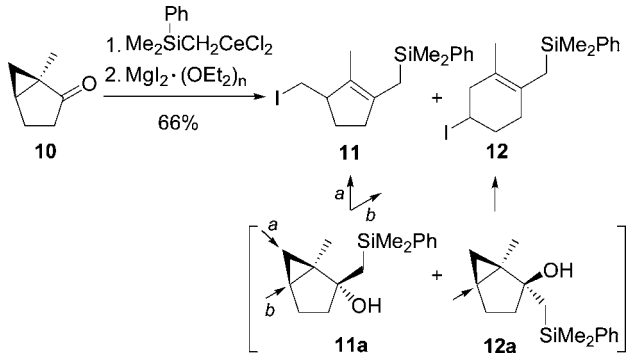
To extend the scope of this approach, some bicyclic cyclopropyl ketone substrates were tested next. As shown in Scheme 4, the (+)-carvone-derived cyclopropyl ketone

Scheme 4



8[9] was transformed into the optically pure bifunctional cyclic allylsilane **9** in a convenient one-pot procedure in good yield as the sole isolable product. Although the corresponding cyclopropyl carbinol intermediate was not isolated, it is safe to suggest its structure as **9a**. 2-Methyl cyclopentenone-derived cyclopropyl ketone **10** was similarly converted into cyclopentenyl allylsilane **11** and ring-expended cyclohexenyl allylsilane **12** in a ratio of 1.2:1 (Scheme 5).[10] Presumably,

Scheme 5



cyclic allylsilanes **11** and **12** might have resulted from the corresponding diastereomeric keto adducts **11a** and **12a**, respectively,[11] where ring-opening of cyclopropane by an iodo anion is assumed to follow a trans anti-periplanar conformational alignment,[12] or from the major adduct **11a** by iodo anion attack on two cyclopropane carbons[4f] as shown (Scheme 5). It is interesting to compare with the Magnus synthesis[13] of endo-cyclic allylsilanes[14] by ring-opening olefin-transposition of silylcyclopropane carbinol derivatives, in which the seven-membered cyclic allylsilanes were formed exclusively (eq 3) regardless of the stereochemistry of the initial silylcyclopropane carbinol. These bifunctional homoiodo allylsilanes (i.e., **9** and **11**) would be potentially useful synthons in natural product synthesis via tandem C−C bond formation (formally an annulation).[15]

To demonstrate the current allylsilane synthesis method in a more functionalized substrate for the aforementioned general strategic plan (Figure 1), the synthesis of an epoxy allylsilane cyclization precursor of type **1** was outlined in Scheme 6. Allylic alcohol **13**, available from **2** by allylic oxidation (SeO_2−TBHP), was epoxidized (Sharpless epoxidation with L-(+)-DET as a chiral ligand) and followed by O-benzylation to afford the epoxy ketone **14** (ca. 50% from **13**). Upon addition of (dimethylphenylsilyl)methyl cerium chloride to epoxy ketone **14** at 0 °C in THF, the desired carbonyl adduct **15** was produced after neutral extractive workup, which without further purification was taken in anhydrous diethyl ether and treated with a freshly prepared solution of MgI_2 etherate (ca. 0.25 M, 1:1 diethyl ether−benzene) at 0 °C for 10 min to give the iodohydrin allylsilane

(9) Cf.: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Chandrasekhar, S.; Narasihmulu, C.; Jagadeshwar, V.; Reddy, K. V. *Tetrahedron Lett.* **2003**, *44*, 3629.

(10) Although inseparable on chromatographic silica gel, they were distinctly identified by ^{1}H NMR.

(11) A pair of diastereomers was spotted on TLC and by ^{1}H NMR analysis of the crude adducts.

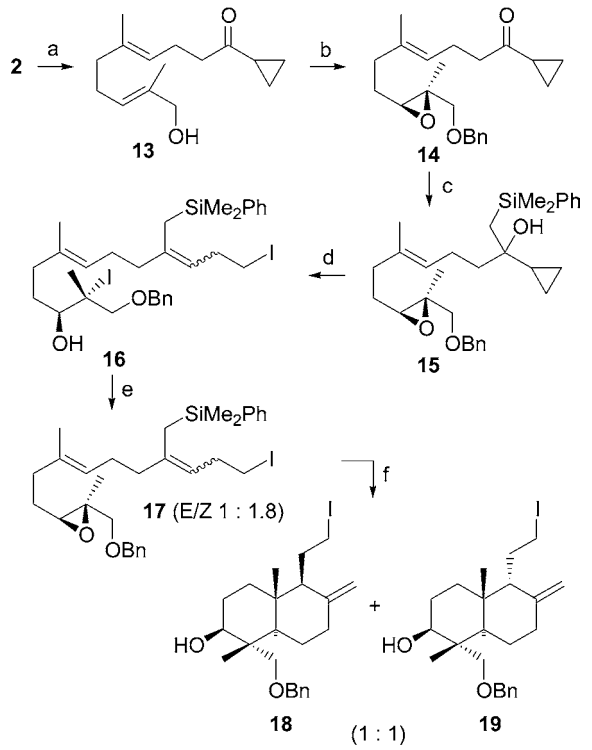
(12) Cf.: Sakaguchi, K.; Fujita, M.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 4313.

(13) (a) Cooke, F.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1978**, 714. (b) Magnus, P.; Cooke, F.; Sarkar, T. *Organometallics* **1982**, *1*, 562.

(14) For an alternative method, see: Kende, A. S.; Hebeisen, P.; Newbold, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 3315.

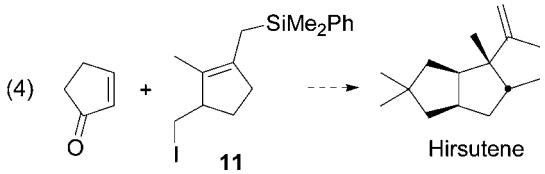
(15) Studies along this line are ongoing in this laboratory; cf. eq 4.

Scheme 6[a]



[a] Conditions: (a) SeO_2, TBHP, CH_2Cl_2, rt, 2 h, 56%. (b) (i) $Ti(O^iPr)_4$, L-(+)-DET, TBHP, CH_2Cl_2, −20 °C, 5 h, 94%; (ii) NaH, BnBr, *n*-Bu_4NI, THF, rt, 1.5 h, 53%. (c) $ClMgCH_2SiMe_2Ph$, $CeCl_3$, THF, 0 °C, 1 h. (d) $MgI_2{\cdot}(OEt_2)_n$, Et_2O, 0 °C, 15 min. (e) K_2CO_3, MeOH, 0 °C, 30 min, 58% from **14**. (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 15 min, 61%.

16 after flash silica gel chromatography.[16] Brief treatment of the allylsilane **16** with K_2CO_3 in methanol at 0 °C gave the epoxy allylsilane **17** as an inseparable mixture of geometric isomers (*Z*/*E* = 1.8:1) in 58% overall yield from epoxy ketone **14**. Exposure of the epoxy allylsilane **17** (mixture of isomers) to BF_3 etherate in CH_2Cl_2 at −78 °C for 15 min and quenching with saturated aqueous sodium bicarbonate at −78 °C furnished the bicyclic product **18** and **19** (61%) as a mixture of two diastereomers (ca. 1:1),[17] which were separable by HPLC (hexane−2-propanol 40:1). The structures of cyclized products **18** and **19** were fully characterized by spectroscopic analysis. We believe this approach would be applicable to the biomimetic synthesis of Labdane diterpenoids in general, and studies on the synthesis of andrographolide,[18] a typical bioactive natural product of this class, are in progress in our laboratory.



In summary, we have developed a novel approach for the synthesis of highly substituted functionalized allylsilanes based on the Julia homoallylic transposition protocol, which features the combination of the incorporation of sterically more hindered and more electron-rich dimethylphenylsilyl grouping and the use of MgI_2 etherate as a unique Lewis acidic reagent. The method is operationally simple (essentially a one-pot procedure),[19] effective, and applicable to bicyclic cyclopropyl ketones and substrates with sensitive functionality (i.e., epoxide). Iodo allylsilanes such as **9** and **11** would be useful bifunctional synthons for the synthesis of terpenoid natural products, as illustrated in eq 4 as an example.[20]

Acknowledgment. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and Fund 20021001) and Ministry of National Education (Funds 99114 and 2000-66) for financial support. The Cheung Kong Scholars program is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**4**, **6**, **7**, **9**, **11**−**14**, and **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) This product was characterized by ^1H NMR and IR spectral analysis. Although MgI_2 was reported as the reagent of choice for iodohydrin synthesis via epoxide ring-opening (cf.: (a) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206. (b) Coutrot, P.; Legris, C. *Synthesis* **1975**, 118) and deoxygenation of epoxide (cf.: Chowdhury, P. K. *J. Chem. Res., Synop*. **1990**, 192), we assumed that the species, i.e., Mg(OH)I, generated from the Julia homoallylic transposition process may serve as the iodo anion source for the production of iodohydrin **16**, in view of the fact that 1 equiv of MgI_2 etherate was used for this transformation.

(17) It is noteworthy that the diastereomeric ratio of the cyclization product **18** and **19** is scrambled in regards to the geometric ratio of epoxy allylsilane precursor **17**, which that implies one of the cyclization conformations (chair-chair vs chair-boat) predominates slightly over the other. Further work will be needed to address this interesting mechanistic aspect through the preparation (or separation) of pure isomeric precursor **17**.

(18) For an earlier synthetic study, see: Pelletier, S. W.; Chappell, R. L.; Prabhakar, S. *J. Am. Chem. Soc.* **1968**, *90*, 2889.

(19) **Typical Procedure for the Preparation of Homoiodo Allysilane from Cyclopropyl Ketone.** Freshly dried (1 mmHg at 150 °C for 7 h from the heptahydrate) $CeCl_3$ (296 mg, 1.2 mmol) was suspended in 10 mL of anhydrous THF, stirred vigorously for 2 h at ambient temperature, and cooled to 0 °C by an ice bath, to which a stock solution of (dimethylphenylsilyl)methylmagnesium chloride in diethyl ether (1.0 M, 1.2 mL, 1.2 mmol) was added dropwise at the same temperature. After the mixture was stirred for 1 h at 0 °C, cyclopropyl ketone (1.0 mmol) in 1 mL of THF was added dropwise and the resulting mixture was warmed gradually to room temperature. When the consumption of starting ketone was complete (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched with water (1 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether. The organic layers were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated carefully in vacuo at 0 °C to give the cyclopropyl carbinol adduct as a light yellowish oil. The crude cyclopropyl carbinol was dried azeotropically with benzene, taken in anhydrous diethyl ether (10 mL) under a nitrogen atmosphere, and stirred at 0 °C, to which a freshly prepared[7c] MgI_2 etherate (1.1 mmol, 0.25 M) solution mixture in Et_2O−benzene (1:1) was added dropwise. The resulting mixture was stirred for 10−15 min at 0 °C, quenched with saturated $NaHCO_3$, and extracted with diethyl ether. The organic extracts were washed with 10% sodiun thiosulfate solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to give an oily residue, which was purified by flash silica gel chromatography eluting with a mixture of diethyl ether−petroleum ether (bp 30−60 °C) to afford the homoiodo allysilane product as a colorless oil.

(20) Cf.: (a) Majetich, G.; Defauw, J. *Tetrahedron* **1988**, *44*, 3833. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855.