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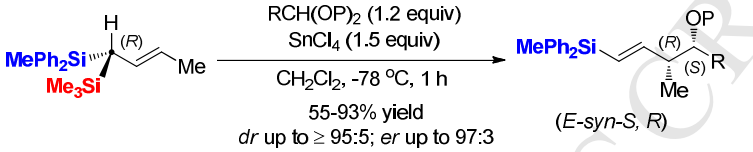

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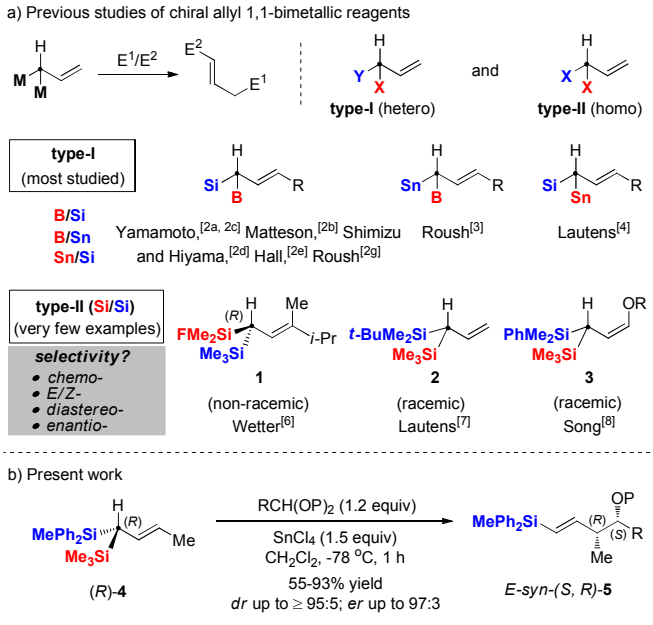
ABSTRACT

Enantioselective synthesis of crotyl geminal bis(silane) **4** has been developed by an asymmetric [1, 5]-hydride shift of allylic hydrazine. $SnCl_4$-promoted Sakurai allylation of (*R*)-**4** with acetals leads to chemoselective desilylation of $SiMe_3$, generating *E-syn*-(*S, R*)-**5** in good yields with high *E/Z*-, diastereo- and enantioselectivity.

1. Introduction

Allyl metallic compounds are very important reagents in organic synthesis.[1] Allylation of aldehydes using these reagents has become one of the most useful methods for controlling the stereochemistry in acyclic systems. The resulting homoallylic alcohols are vital building blocks in the synthesis of biologically active molecules such as macrolides and polyether antibiotics. Despite the typical allylation reagents are mono-metal-substituted, bimetallic species appears being more attractive for rapid increasing the structural complexity. In the allyl bimetal family, 1, 1-bimetallic compound is a unique member. Distinct from 1, 2- and 1, 3-types (not shown), 1, 1-type contains two metals attached into one carbon center. Because two C−M bonds share with the same allylic moiety, 1, 1-type allyl bimetallic reagent could play as a linchpin to assemble electrophiles E^1 and E^2 by sequential functionalization at 3- and 1-positions (Scheme 1a, top left). When two metal moieties are different, the carbon they attached would be a stereogenic center. Thus, chemoselective cleaving one of the C−M bonds becomes crucial for realizing effective chirality transfer. To do so, previous studies have been largely focused on hetero-bimetallic compounds possessing two different metal centers such as B/Si,[2] B/Sn[3] and Sn/Si[4] (Scheme 1a, type-I). In the combination of B/Si, due to the C−B bond is weaker than the C−Si bond, chemoselective elimination of the more reactive C−B bond could be achieved during the allylation with aldehydes.



Scheme 1. (a) Previous studies on chiral allyl 1, 1-hetero- and homo-bimetallic reagents; (b) asymmetric Sakurai allylation of acetals using crotyl geminal bis(silane) (*R*)-**4**.

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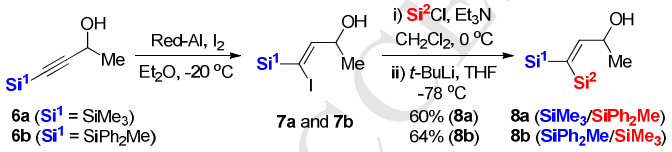
Compared with allyl 1, 1-hetero-bimetals, the corresponding chiral homo-bimetallic reagents (Scheme 1a, type-II) such as allyl geminal bis(silanes) have been investigated in a very limited scope. Both metal centers in these compounds are silicon, but with different substitution modes. Imaginably, it would be difficult to selectively cleavage one of the C−Si bonds if only by differentiating the substituents on silicon. That would make the chirality transfer[5] more challenging than that using hybrid combination such as B/Si. To the best of our knowledge, there is only one successful example utilizing optically active **1** featuring a $SiMe_3/SiMe_2F$ combination. As reported by Wetter,[6] **1** underwent asymmetric acylation with CH_3COCl through chirality transfer enabled by chemoselective desilylation of $SiMe_2F$. There are other two examples using racemic **2** ($SiMe_3/SiMe_2t$-Bu) reported by Lautens,[7] and racemic **3** ($SiMe_3/SiMe_2Ph$) reported by our group.[8a] Despite selective desilylation of $SiMe_3$ was observed in these two cases, no asymmetric chirality transfer was involved since **2** and **3** are racemic. Overall, the potential values of optically active allyl geminal bis(silanes) in organic synthesis are still poorly unexplored. A series of selectivity issues have not been fully understood in these reagents-involved allylation with electrophiles.

Herein we report the enantioselective synthesis of crotyl geminal bis(silane) **4** by an asymmetric [1, 5]-hydride shift of allylic hydrazine. $SnCl_4$-promoted Sakurai allylation[9] of (*R*)-**4** with acetals leads to chemoselective desilylation of $SiMe_3$, generating *E*-*syn*-(*S*, *R*)-**5** in good yields with high *E*/*Z*-, diastereo- and enatioselectivity (Scheme 1b).

2. Results and discussion

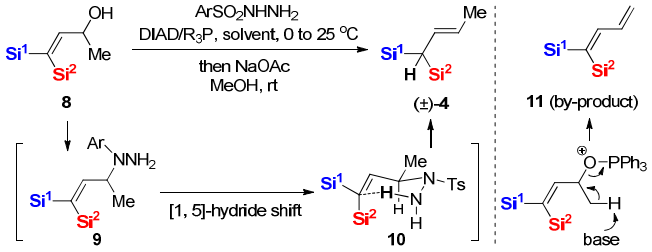
The key strategy for the synthesis of crotyl geminal bis(silane) **4** relies on a sigmatropic [1, 5]-hydride shift of allylic hydrazine. The requisite bis(silyl) allylic alcohols **8** were initially synthesized in racemic form by the procedure shown in Scheme 2. Propargyl alcohol **6** was reduced with Red-Al to afford the corresponding *Z*-vinyl aluminum species, which was trapped with iodine to afford *Z*-vinyl silane **7**.[10] Silylation of **7** followed by *t*-BuLi-promoted retro-[1, 4]-Brook rearrangement[11] delivered allylic alcohols **8a** and **8b**, respectively, in 60% and 64% overall yields by three steps. Allylic alcohol **8a** contains *E*-$SiMe_3$ and *Z*-$SiPh_2Me$, while these two silyl groups in **8b** are switched to each other.



Scheme 2. Synthesis of racemic **8a** and **8b**.

Transformation of alcohol **8** into racemic crotyl geminal bis(silane) (±)-**4** involves Mitsunobu reaction to generate the hydrazine intermediate **9** followed by NaOAc-promoted [1, 5]-hydride shift (**10**).[12] The approach was first examined using **8a** and $TsNHNH_2$ with DIAD/PPh_3 in THF (Table 1, entry 1). The initially formed allylic hydrazine **9** underwent clean [1, 5]-hydride shift by treatment with NaOAc in MeOH. The desired silane (±)-**4** was obtained in 30% overall yield. The moderate yield of the approach was attributed to the low efficiency of Mitsunobu reaction. Besides some undefined side-paths, a based-promoted elimination of the oxyphosphonium intermediate was observed to generate the major by-product diene **11a** in 20% yield. No Mitsunobu reaction occurred using CH_3NO_2 or NMM

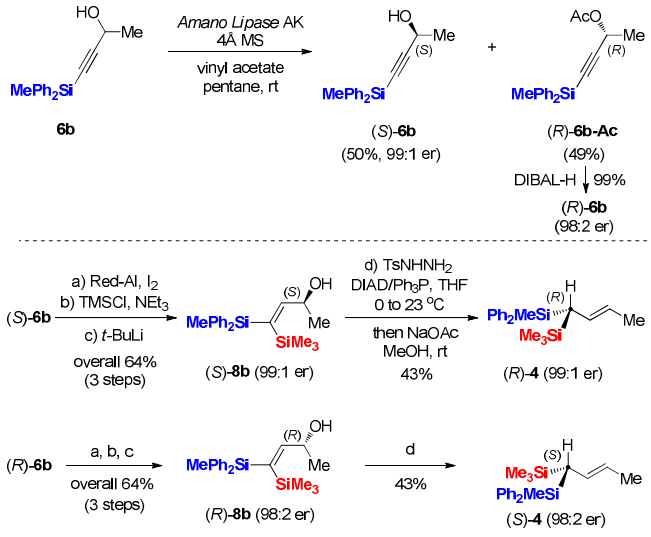
Table 1. Screening of Mitsunobu reaction conditions.[a]



entry	**8**	Ar	solvent	PR_3	(±)-**4**[b]	**11**[b]
1	**8a**	*p*-Me-C_6H_4	THF	PPh_3	30%	**11a**(20%)
2	**8a**	*p*-Me-C_6H_4	CH_3NO_2	PPh_3	N. R.	N. R.
3	**8a**	*p*-Me-C_6H_4	NMM	PPh_3	N. R.	N. R.
4	**8a**	*o*-NO_2-C_6H_4	THF	PPh_3	N.R.	N.R.
5	**8a**	*p*-Me-C_6H_4	THF	P(*t*-Bu)$_3$	N. R.	N. R.
6	**8b**	*p*-Me-C_6H_4	THF	PPh_3	43%	**11b**(10%)

[a] Reaction conditions: **8** (0.6 mmol), $ArSO_2NHNH_2$ (1.2 mmol), Ph_3P (1.2 mmol) and DIAD (1.2 mmol) in THF (6.0 mL) at 0 °C to 25 °C for 2 h; then NaOAc (0.9 mmol) in MeOH (4.0 mL) at rt for 24 h. [b] Isolated yields after purification by silica gel column chromatography.

as solvent (entries 2 and 3), or switching the sulfonyl substituent from Ts to Ns (entry 4), or replacing PPh_3 with P(*t*-Bu)$_3$ (entry 5). Compared with **8a**, the approach using **8b** increased the yield of (±)-**4** to a useful level of 43% (entry 6). Formation of the by-product **11b** was suppressed in an acceptable 10% yield. The increased efficiency might be explained by the different steric effect of the *Z*-silyl group in **8a** and **8b**. Because **8b** contains a smaller *Z*-$SiMe_3$ group, the S_N2 substitution with hydrazine should be easier to proceed than that of **8a** containing a larger *Z*-$SiPh_2Me$ group.

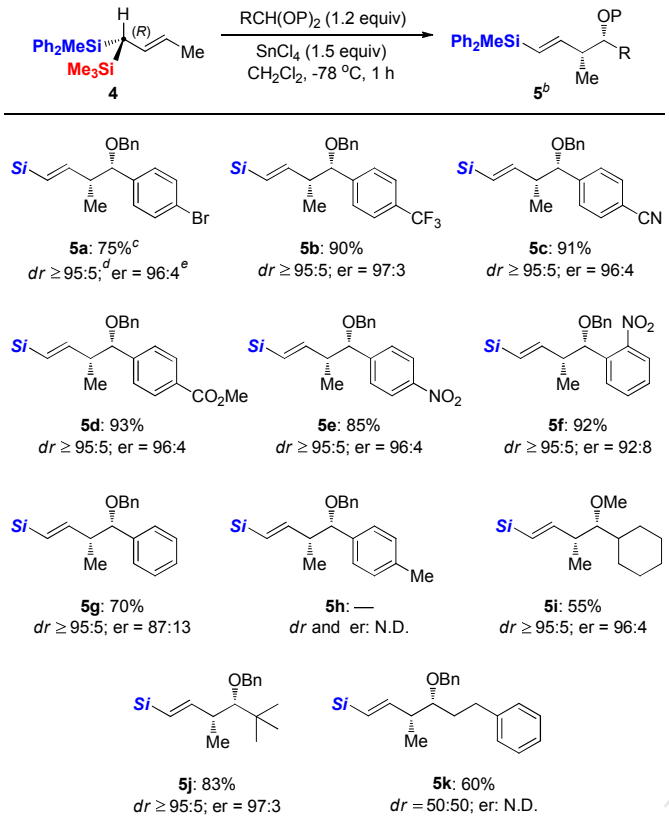


Scheme 3. Enantioselective synthesis of crotyl geminal bis(silane) **4**.

With the optimal [1, 5]-hydride shift condition in hand, the enantioselective synthesis of **4** was carried out (Scheme 3). The preparation commenced with lipase-catalyzed kinetic resolution of **6b** to provide (*S*)-**6b** in 50% yield with 99:1 *er*.[13] The (*R*)-**6b-Ac** was generated in 49% yield, and was directly reduced with DIBAL-H to afford (*R*)-**6b** quantitatively with 98:2 *er*. Following the same procedure as that used for racemic **6b**, allylic alcohol (*S*)-**8b** was obtained in 64% yield without loss of enantioselectivity. The Mitsunobu reaction/[1, 5]-hydride shift process of (*S*)-**8b** subsequently delivered (*R*)-**4**[14] in 43% yield

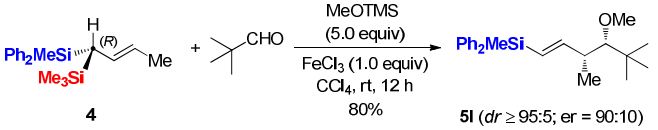
with 99:1 *er*. The process was also applied to the synthesis of (*S*)-**4** from the corresponding (*R*)-**6b**. Both (*R*)- and (*S*)-**4** are stable to moisture, and were prepared on gram scale and purified easily by silica gel column.

Table 2. Asymmetric Sakurai Allylation of (*R*)-**4** with Acetals.[a]



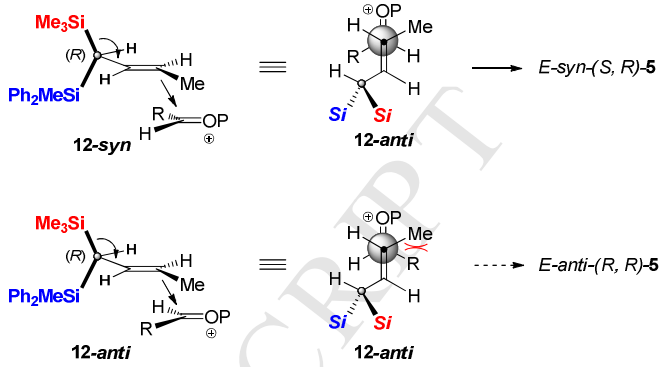
[a] Reaction conditions: (*R*)-**4** (0.15 mmol), acetal (0.18 mmol) and $SnCl_4$ (0.23 mmol) in CH_2Cl_2 (3.0 mL) at -78 °C for 1 h. [b] The *syn*-(*S*, *R*)-stereochemistry of the product was assigned by transforming **5a** to the known compound. See supporting information for details. [c] Isolated yields after purification by silica gel column chromatography. [d] The ratios were determined by ^{1}H NMR spectroscopy of the crude products. [e] The ratios were determined by HPLC analysis using a chiral stationary phase.

The Sakurai allylation of (*R*)-**4** with acetals was next examined (Table 2). After screening a range of Lewis acids, $SnCl_4$ appears most effective to promote the reaction in CH_2Cl_2 at -78 °C. While chemoselective desilylation of the more reactive $SiMe_3$ occurred in all cases to give $SiPh_2Me$ substituted *E*-alkene, the nature of acetals has great impacts on the diastereo- and enantioselectivity. Reaction of aryl acetals containing an electron-withdrawing group gave rise to **5a**-**5f** as a single *syn*-diastereomer. Moreover, the chirality transfer from geminal bis(silyl) moiety to the products proceeded reliably to give excellent (*S*, *R*)-enantioselectivity. However, a severe decreasing of *er* was observed when using phenyl acetals to form **5g**. In addition, substitution of an electron-donating Me group on the phenyl ring inhibited the allylation to give the desired **5h**. The reaction was suitable for Cy- and *t*-Bu-substituted acetals, giving **5i** and **5j** in high *dr* and *er*. But, a poor *dr* of 50:50 was detected in the formation of **5k** from less sterically demanding unbranched alkyl acetal.



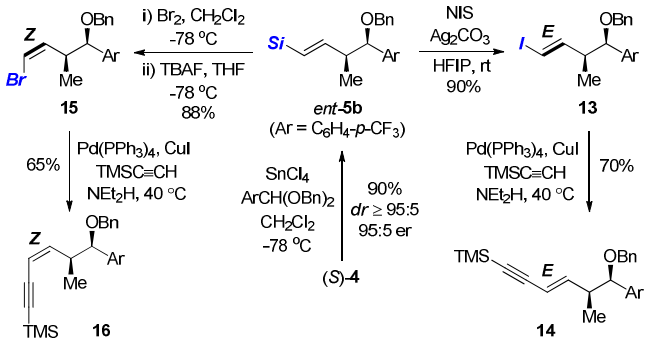
Scheme 4. One-pot acetalation/Sakurai allylation to form **5l**.

Using $FeCl_3$ as Lewis acid allowed us to realize a one-pot acetalation/Sakurai allylation process (Scheme 4).[15] The reaction was performed simply by mixing (*R*)-**4**, *t*-BuCHO, $MeOSiMe_3$ and $FeCl_3$ in CCl_4 at room temperature for 12 h. The desired Sakurai allylation product **5l** was generated as a single *syn*-diastereomer in 80% yield with a 90:10 *er*.



Scheme 5. Model analysis to explain the selectivity outcomes.

As shown in Table 2, our approach achieved four different selectivities in a single transformation: elimination of $SiMe_3$ over $SiMe_2Ph$ (*chemoselectivity*), *E*- over *Z*-vinyl silane (*geometrical selectivity*), *syn*- over *anti*-allylation (*diastereoselectivity*) and *S*/*R* over *R*/*S* (*enantioselectivity*). A model in Scheme 5 was proposed to rationalize the above selectivity outcomes. Firstly, the reactive conformation of (*R*)-**4** should be that which minimizes allylic strain, and also benefits from a dual hyperconjugation effect between the two C−Si bonds and alkene. Chemoselective elimination of the more reactive C−$SiMe_3$ bond would generate $SiPh_2Me$-substituted alkene with *E*-configuration. Secondly, based on the classical *anti*-S_E' mechanism, the oxacarbenium should approach to the 3-position of (*R*)-**4** by the orientation antiperiplanar to the eliminating C-$SiMe_3$ bond.[16] In the resulted two "open" transition states **12-*syn*** and **12-*anti***, **12-*syn*** appears being more favorable than **12-*anti***, which suffers from a gauche interaction between Me and R groups. Thus, reaction via **12-*syn*** would generate *E*-*syn*-(*S*, *R*)-**5** predominantly.



Scheme 6. Transformation of *ent*-**5b** into *E*-enyne **14** and *Z*-enyne **16**.

The resulting *E*-vinyl silane moiety was utilized as the second functionality of geminal bis(silane), leading to divergent synthesis of *E*- and *Z*-enynes. As shown in Scheme 6, *ent*-**5b**, generated from (*S*)-**4**, underwent Ag_2CO_3-promoted iodination with NIS to provide *E*-vinyl iodide **13** in 90% yield.[17] The subsequent Sonogashira cross-coupling[18] with terminal alkyne gave rise to *E*-enyne **14** in 70% yield. On the other hand, dibromination of *ent*-**5b** followed by elimination of $MePh_2SiBr$

with TBAF led to *Z*-vinyl bromide **15** in 88% yield.[19] Sonogashira cross-coupling of **15** with terminal alkyne then afforded *Z*-enyne **16** in 65% yield.

3. Conclusion

In summary, we have described the enantioselective synthesis of crotyl geminal bis(silane) **4** by an asymmetric [1, 5]-hydride shift of allylic hydrazine. Chemoselective desilylation of $SiMe_3$ was realized in the Sakurai allylation with acetals, leading to $MePh_2Si$-substituted *E-syn*-(*S, R*)-**5** in good yields with high *E/Z*-, diastereo- and enatioselectivity. More applications of this new allyl silane reagent in organic synthesis are underway.

4. Experimental section

Commercial reagents were used without any purification. All reactions were performed using common anhydrous, inert atmosphere techniques. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (HSGF-254). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a staining solution of $KMnO_4$ stains, $H_3PO_4 \cdot 12MoO_3$/EtOH stains, H_2SO_4 (conc.)/anisaldehyde/EtOH stains. Product purifications were performing using Silica Gel (200-300 mesh) for column chromatography. ^1H NMR spectra were recorded at 400 MHz (Varian) and 600 MHz (Agilent), and ^{13}C NMR spectra were recorded at 100 MHz (Varian) and 150 MHz (Agilent) using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Infrared spectra were obtained using KCl plates on a VECTOR22. High-resolution mass spectral analyses performed on Waters Q-TOF. In each case, enantiomeric ratio was determined by HPLC analysis on a chiral column in comparison with racemates, using a Daicel Chiralpak IA Column (250 × 4.6 mm) or Chiralpak IC Column (250 × 4.6 mm), Chiralpak OD-H Column (250 × 4.6 mm). UV detection was monitored at 220 nm or 254 nm. Optical rotation was examined in $CHCl_3$ solution at 20 °C. Pentane, CH_3NO_2, NMM, CH_2Cl_2, CCl_4, Et_2NH and Et_3N were distilled from CaH_2. Et_2O and THF were distilled from sodium.

*4.1. Synthesis of (S)-**6b***

To a 0.5 M pentane solution of racemic **6b** (20.6 g, 37.6 mmol) was added *Amano lipase AK* (2.2 g, 18.8 mmol) and vinyl acetate (58 mL, 188 mmol). The resulting suspension was stirred at room temperature for 24 h under argon atomosphere. The mixture was filtered via celite. The filtration was concentrated and purified by silica gel chromatography (10% EtOAc/petroleum ether) to provide (*S*)-**6b** (10.3 g, 50%) as a colorless oil. R_f = 0.51 (EtOAc-petroleum ether, 1:10) ; $[\alpha]_D^{20}$ = -13.9 (*c* 1.0, $CHCl_3$); The enantiomeric ratio was determined to be 99:1 by HPLC analysis on Chiralpak IC column (1% 2-propanol/*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 18.33 min, t_{major} = 19.77 min; ^1H NMR (600 MHz, $CDCl_3$), δ 7.65-7.66 (m, 4H), 7.38-7.44 (m, 6H), 4.62 (q, *J* = 6.6 Hz, 1H), 2.11 (s, 1H, OH), 1.53 (d, *J* = 6.6 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.9, 134.5 134.4, 129.7, 127.9, 110.9, 84.8, 58.8, 24.1, -2.1. IR (liquid film) cm^{-1} 3310, 3069, 2962, 2172, 1428, 1370, 1325, 1259, 1113, 1042, 788; HRMS (MALDI, m/z) calcd for $C_{17}H_{18}NaOSi$ $(M+Na)^+$: 289.1019, found 289.1021.

*4.2. Synthesis of (S)-**8b***

To a solution of (*S*)-**6b** (10.8 g, 40.6 mmol) in Et_2O (500 mL) was added Red-Al (11.9 mL, 60.9 mmol) dropwise at 0 °C. After stirring for 8 h, I_2 (15.5 g, 60.9 mmol) was added at –20 °C. The resultant mixture was stirred at room temperature overnight before quenching with sat aq NH_4Cl (200 mL) and extracted with Et_2O (3 × 200 mL). The combined layers were washed with sat aq $Na_2S_2O_3$ (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-1.0% of EtOAc/petroleum ether) afforded vinyl iodine intermediate (13.6 g, 85%) as a yellow oil. To a solution of the above vinyl iodine (10.0 g, 25.4 mmol), Et_3N (10.5 mL, 76.2 mmol) and DMAP (310 mg, 2.6 mmol) in CH_2Cl_2 (120 mL) was added TMSCl (3.8 mL, 30.4 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with sat aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide crude silyl ether. To a solution of the above silyl ether (2.0 g, 4.3 mmol) in THF (50 mL) was added *t*-BuLi (6.6 mL of 1.3 M solution in pentane, 8.6 mmol) dropwise via syringe at -78 °C under argon atmosphere. The reaction was allowed to proceed for 30 min at -78 °C. The resultant solution was warmed to room temperature and stirred for another 30 min before quenching with sat aq NH_4Cl (20 mL) and extraction with ether (3 × 20 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-1.0% of EtOAc/petroleum ether) afforded (*S*)-**8b** (1.1 g, 64% for 3 steps) as a yellow oil. R_f = 0.51 (EtOAc-petroleum ether, 1:10) ; $[\alpha]_D^{20}$ = -18.6 (*c* 1.0, $CHCl_3$); The enantiomeric ratio was determined to be 99:1 by HPLC analysis on Chiralpak IA column (0.25% 2-propanol/*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 21.95 min, t_{major} = 30.63 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.47 (m, 4H), 7.33-7.34 (m, 6H), 6.42 (d, *J* = 8.8 Hz, 1H), 4.62-4.69 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.68 (s, 3H); 0.05 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 138.1, 137.0 136.9, 135.0, 134.9, 129.1, 129.0, 127.7, 89.2, 22.7, 2.0, -2.3; IR (liquid film) cm^{-1} 2960, 2919, 1568, 1428, 1262, 1249, 1110, 1052, 1027, 941, 907, 837; HRMS (MALDI, m/z) calcd for $C_{20}H_{28}NaOSi_2$ $(M+Na)^+$: 363.1571, found 363.1575.

*4.3. Synthesis of (R)-**4***

To a solution of Ph_3P (6.4 g, 34.1 mmol) in dry THF (100 mL) was added diisopropoylazodicarboxylate (DIAD, 6.8 mL, 34.1 mmol) at 0 °C. A solution of *(S)*-**8b** (5.8 g, 17.1 mmol) in dry THF (200 mL) and $TsNHNH_2$ (6.35 g, 34.1 mmol) were then added sequentially to the above mixture at 0 °C. The reaction was warmed to room temperature and allowed to stand for 2 h. The resultant solution was partitioned with Et_2O (50 mL) and H_2O (50 mL). The organic layers were washed with 50 mL of H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Filtration of the residue by silica gel column chromatography provided the crude allylic hydrazine. To a solution of the above allylic hydrazine (3.8 g, 7.5 mmol) in MeOH (5 mL) was added NaOAc (1.23 g, 15 mmol) at room temperature. After stirring for 24 h, MeOH was removed under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to afford (*R*)-**4** (2.4 g, 43%) as a clear oil. R_f = 0.68 (EtOAc-petroleum ether, 0:1); $[\alpha]_D^{20}$ = -36.4 (*c* 1.0, $CHCl_3$); The enantiomeric ratio was determined to be 99:1 by HPLC analysis on Chiralpak IG-RH column (CH_3OH/H_2O = 90/10, 0.4 mL/min), UV 205 nm, t_{major} = 14.85 min, t_{minor} = 16.60 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.56 (m, 4H), 7.33-7.36 (m, 6H), 5.38 (dd, J_1 = 11.2 Hz, J_2 = 14.8 Hz, 1H), 5.21 (dq, J_1 = 6.4 Hz, J_2 = 14.8 Hz, 1H), 1.72 (q, *J* = 11.2 Hz, 1H), 1.63 (d, *J* = 6.4 Hz, 3H), 0.63 (s, 3H), -0.15 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 137.7, 135.0, 134.9, 134.8, 128.9, 128.8, 127.6, 127.4, 124.2, 22.0, 18.2, 0.5, -3.3; IR (liquid film) cm^{-1} 3010, 2955, 2915, 1427, 1248, 1105, 1052, 1024, 857, 770; HRMS (MALDI, m/z) calcd for $C_{20}H_{28}NaSi_2$ $(M+Na)^+$: 347.1622, found 347.1625.

*4.4. Synthesis of **5a***

To a solution of (*R*)-**4** (50 mg, 0.15 mmol) and *p*-Br-$C_6H_4CH(OBn)_2$ (59 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added $SnCl_4$ (26 μL, 0.23 mmol) at –78 °C under argon atmosphere. After stirring for 1 h, the reaction was quenched with sat aq $NaHCO_3$ (5 mL) and extract with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **5a** (61 mg, 75%) as a yellowish oil. R_f = 0.55 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = -32.2 (*c* 1.0, $CHCl_3$); The enantiomeric ratio was determined to be 95:5 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 1.0 mL/min), UV 220 nm, t_{major} = 28.50 min, t_{minor} = 36.08 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.26-7.38 (m, 15H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.90 (dd, J_1 = 7.2 Hz, J_2 = 18.4 Hz, 1H), 5.77 (d, *J* = 18.4 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* =7.2 Hz, 1H), 2.62-2.70 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 139.8, 138.2, 136.6, 136.5, 134.7, 134.6, 131.3, 129.3, 129.2, 129.1, 128.3, 127.8, 127.7, 127.6, 127.5, 126.3, 121.3, 84.4, 70.6, 47.5, 16.0, -3.8; IR (liquid film) cm^{-1} 2960, 2918, 2851, 1742, 1428, 1217, 1112, 1070, 1011, 754; HRMS (ESI-TOF, m/z) calcd for $C_{31}H_{31}BrNaOSi$ $(M+Na)^+$: 549.1220, found 549.1226.

*4.5. Synthesis of **5l***

To a solution of (*R*)-**4** (50 mg, 0.15 mmol), trimethyl acetaldehyde (20 μL, 0.18 mmol) and MeOTMS (0.18 mL, 0.77 mmol) in CCl_4 (0.5 mL) was added anhydrous $FeCl_3$ (25 mg, 0.15 mmol) at room temperature. After stirring for 12 h, the reaction was quenched with sat aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **5l** (43 mg, 80 %) as a yellow oil. R_f = 0.50 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = -5.4 (c = 1.0 in $CHCl_3$); The enantiomeric ratio was determined to be 90:10 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 0.7 mL/min), UV 220 nm, t_{major} = 6.01 min t_{minor} = 6.28 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.51 (m, 4H), 7.34-7.39 (m, 6H), 6.21 (dd, J_1 = 6.8 Hz, J_2 = 18.4 Hz, 1H), 5.92 (d, *J* = 18.4 Hz, 1H), 3.36 (s, 3H), 2.75 (d, *J* = 4.0 Hz, 1H), 2.56-2.62 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H); 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 137.0, 136.9, 134.8, 129.7, 127.7, 122.5, 92.5, 61.5, 42.2, 36.9, 27.0, 15.5, -3.7; IR (liquid film) cm^{-1} 2956, 2927, 2859, 1615, 1428, 1260, 1216, 1106, 1082, 1030, 797; HRMS (ESI-TOF, m/z) calcd for $C_{23}H_{32}NaOSi$ $(M+Na)^+$: 375.2115, found 375.2111.

*4.6. Synthesis of **13***

To a solution of *ent*-**5b** (100 mg, 0.19 mmol) in anhydrous HFIP (5.0 mL) were added Ag_2CO_3 (16 mg, 0.058 mmol) and NIS (52 mg, 0.23 mmol) under argon atmosphere at room temperature. After stirring for 2 h, the reaction was quenched with sat aq $Na_2S_2O_3$ (5.0 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **13** (78 mg, 90%) as a yellow oil. R_f = 0.55 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = 12.6 (*c* 1.0 in $CHCl_3$); The enantiomeric ratio was determined to be 94:6 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 13.53 min, t_{major} = 17.24 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.28-7.39 (m, 7H), 6.43 (dd, J_1 = 8.0 Hz, J_2 = 14.4 Hz, 1H), 5.92 (d, *J* = 14.4 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 8.4 Hz, 1H), 2.53-2.61 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 144.0, 137.8, 128.4, 128.3, 127.8, 127.7, 127.6, 125.2 (CF_3, q, $J_{C\text{-}F}$ = 3.8 Hz), 83.3, 76.1, 70.8, 47.0, 14.6, -1.1; IR (liquid film) cm^{-1} 2971, 2915, 2850, 1455, 1325, 1251, 1215, 1166, 1128, 1067, 1018, 960, 842; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{18}F_3INaO$ $(M+K)^+$: 484.9986, found 484.9990.

*4.7. Synthesis of **14***

To a solution of **13** (65 mg, 0.15 mmol) in Et_2NH (2 mL) was added CuI (2.7 mg, 0.014 mmol), $Pd(PPh_3)_4$ (8.4 mg, 0.007 mmol). The solution was degassed by three-pump-taw cycles followed by adding ethynyltrimethylsilane (82 μL, 0.83 mmol). The resulting mixture was refluxed at 40 °C before complete conversion of the starting material as monitored by TLC. The reaction was quenched with sat aq NH_4Cl (2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **14** (42 mg, 70%) as a yellow oil. R_f = 0.56 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = 1.9 (*c* 1.0 in $CHCl_3$); The enantiomeric ratio was determined to be 95:5 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 11.79 min, t_{major} = 12.56 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28-7.37 (m, 5H), 6.08 (dd, J_1 = 7.6 Hz, J_2 = 16.0 Hz, 1H), 5.41 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 6.4 Hz, 1H), 2.57-2.66 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 144.2, 138.0, 128.4, 127.7, 127.6, 127.5, 125.2 (CF_3, q, $J_{C\text{-}F}$ = 3.8 Hz), 110.5, 103.7, 93.7, 83.8, 70.9, 44.0, 15.0, -0.07; IR (liquid film) cm^{-1} 2969, 2916, 2848, 1455, 1325, 1250, 1165, 1127, 1066, 841, 757; HRMS (ESI-TOF, m/z) calcd for $C_{24}H_{27}F_3NaOSi$ $(M+Na)^+$: 439.1675, found 439.1677.

*4.8. Synthesis of **15***

To a solution of *ent*-**5b** (100 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added Br_2 (11 μL, 0.20 mmol) at –78 °C under argon atmosphere. After stirring for 30 min, the reaction was quenched with sat aq $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification. To a solution of the above crude product in THF (5 mL) was added TBAF (0.25 mL, 0.25 mmol, 1.0 M solution in THF) at –78 °C under argon atmosphere. After stirring for 30 min, the reaction was quenched with sat aq $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **15** (66 mg, 88%) as a yellowish oil. R_f = 0.55 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = 92.8 (*c* 1.0 in $CHCl_3$); The enantiomeric ratio was determined to be 95:5 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 10.57 min, t_{major} = 13.15 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.31-7.38 (m, 5H), 6.08 (d, *J* = 7.2 Hz, 1H), 6.02 (dd, J_1 = 7.2 Hz, J_2 = 8.8 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 6.4 Hz, 1H), 4.28 (d, *J* = 12.0 Hz, 1H),

3.06-3.11 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 138.0, 136.6, 128.4, 127.7, 127.6, 127.5, 125.2 (CF_3, q, $J_{C\text{-}F}$ = 3.8 Hz), 107.9, 83.1, 71.1, 41.5, 14.4; IR (liquid film) cm^{-1} 2971, 2919, 2867, 1619, 1454, 1418, 1323, 1261, 1163, 1123, 1066, 1017, 834; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{18}BrF_3KO$ $(M+K)^+$: 437.0125, found 437.0120.

4.6. Synthesis of ***16***

To a solution of **15** (65 mg, 0.16 mmol) in Et_2NH (2 mL) was added CuI (3 mg, 0.016 mmol), $Pd(PPh_3)_4$ (9.4 mg, 0.08 mmol). The solution was degassed by three-pump-taw cycles followed by adding ethynyltrimethylsilane (92 μL, 0.65 mmol). The resulting mixture was refluxed at 40 °C before complete conversion of the starting material as monitored by TLC. The reaction was quenched with sat aq NH_4Cl (2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0-0.5% of EtOAc/petroleum ether) afforded **16** (44 mg, 65%) as a yellow oil. R_f = 0.55 (EtOAc-petroleum ether, 1:40); $[\alpha]_D^{20}$ = 78.4 (*c* 1.0 in $CHCl_3$); The enantiomeric ratio was determined to be 94:6 by HPLC analysis on Chiralpak OD-H column (*n*-hexane, 1.0 mL/min), UV 220 nm, t_{minor} = 6.94 min, t_{major} = 8.88 min; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.29-7.37 (m, 5H), 5.83 (dd, $J_1 = J_2$ = 10.2 Hz, 1H), 5.41 (d, J = 10.2 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 6.0 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H), 3.16-3.22 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.5, 147.8, 138.1, 128.4, 127.7, 127.6, 127.5, 125.1 (CF_3, q, $J_{C\text{-}F}$ = 3.8 Hz), 109.6, 101.6, 99.1, 84.0, 71.2, 41.8, 15; IR (liquid film) cm^{-1} 2963, 2920, 2848, 1325, 1261, 1215, 1166, 1066, 1017, 805; HRMS (ESI-TOF, m/z) calcd for $C_{24}H_{27}F_3NaOSi$ $(M+Na)^+$: 439.1675, found 439.1677.

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Supplementary Material

Supplementary data (^{1}H NMR, ^{13}C NMR, IR, HRMS spectra of new compounds) related to this article can be found online.

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14. The *R*-configuration of (*R*)-**4** was assigned by comparing its circular dichroism spectroscopy with the computational results. See Supporting Information for details. This assignment can be also supported by the following well-known stereochemical course. Mitsunobu reaction of (*S*)-**8b** with hydrazine would give (*R*)-**9b** with inversion of the configuration. 1, 5-hydride shift of

(*R*)-**9b** by a six-membered chair-like transition state should afford (*R*)-**4**.

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