JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

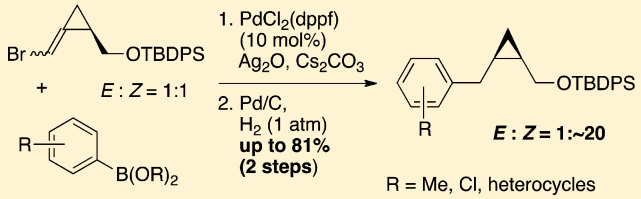
Preparation of Chiral Bromomethylenecyclopropane and Its Use in Suzuki–Miyaura Coupling: Synthesis of the Arylmethyl-(*Z*)-cyclopropane Structure Core

Makoto Tanabe,[†] Mizuki Watanabe,[†] Naoyuki Hoshiya,[†] Akira Mizuno,[†] Hayato Fukuda,[†] Mitsuhiro Arisawa,*[,†,§] and Satoshi Shuto*[,†,‡]

[†]Faculty of Pharmaceutical Sciences and [‡]Center for Research and Education on Drug Development, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

Supporting Information

ABSTRACT: A preparative method for an optically active bromomethylenecyclopropane unit and its practical conversion to (*Z*)-cyclopropane-containing chiral compounds via Suzuki–Miyaura coupling were established.



INTRODUCTION

The importance of strained carbocycles, such as three-membered rings, has long been recognized in organic chemistry.[1] In addition, interest in small carbocycles is growing in the related fields of medicinal and biological chemistry.[2] The prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to search for novel and diverse approaches to their synthesis.[3] Moreover, because the use of rigid structures based on sp^3 carbons is now a key topic in drug design in terms of improved selectivity,[4] nonracemic compounds with a cyclopropane ring play an important role in medicinal research.

We are interested in a series of chiral arylmethylcyclopropanes comprising *Z* types **I** and *ent*-**I** and *E* types **II** and *ent*-**II**, as sp^3-carbon-based rigid-core structures for medicinal chemical studies, as shown in Figure 1.

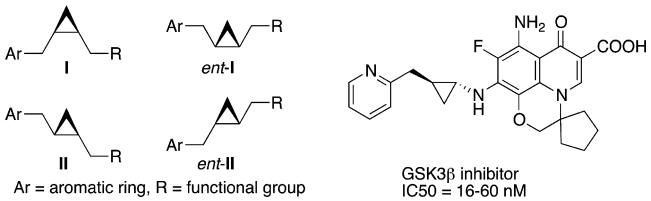


Figure 1. General structures of chiral arylmethylcyclopropanes and a medicinal example.

The synthesis of these nonracemic compounds with a (*Z*)-cyclopropane is challenging in organic chemistry.[5] We thought that chiral bromomethylenecyclopropane **1** should be a versatile precursor for synthesizing various nonracemic (*Z*)-arylmethylcyclopropanes **I** and *ent*-**I**. Among the classes of cyclopropanes, methylenecyclopropane and alkylidenecyclopropane derivatives are well documented as useful synthetic intermediates in organic chemistry,[6] but the synthetic utility of bromomethylenecyclopropane has not yet been established.

Considering the importance of chiral bromomethylenecyclopropane toward nonracemic natural and/or unnatural (*Z*)-cyclopropane-containing (complex) molecular targets, we report herein a preparation of chiral bromomethylenecyclopropane and its use in Suzuki–Miyaura coupling. To the best of our knowledge, there are no reports of nonracemic bromomethylenecyclopropane derivatives, and this is the first example of Suzuki–Miyaura coupling of a bromomethylenecyclopropane.

RESULTS/DISCUSSION

We used cyclopropane as the key unit (Figure 2) to design conformationally restricted analogues of bioactive ligands based

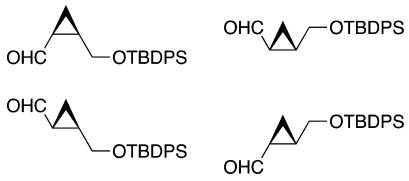


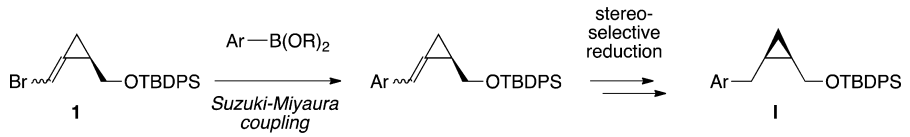
Figure 2. Our reported chiral cyclopropane units.

on a spatial screening concept to search for unknown bioactive conformations of ligands.[7] However, there is a difficulty in synthesizing molecules whose cyclopropane and aromatic ring, including nitrogen-containing heterocycles, are connected by a C1 unit, methylene, from these cyclopropane units. We envisioned that the novel chiral bromomethylenecyclopropane

Received: August 1, 2013
Published: November 8, 2013

dx.doi.org/10.1021/jo401675z | J. Org. Chem. 2013, 78, 11714–11720

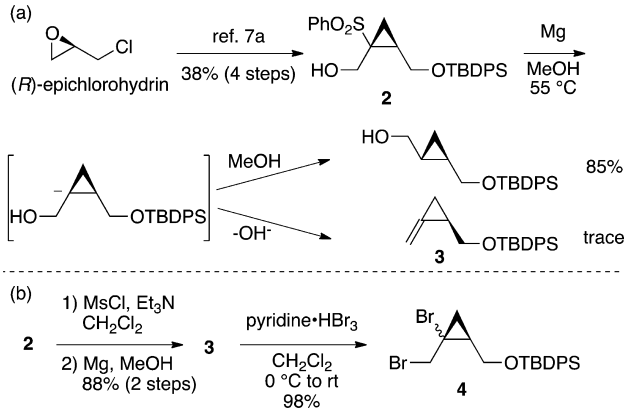
Scheme 1. Our Chiral Bromomethylenecyclopropane Unit and Its Use in Suzuki–Miyaura Coupling



unit **1** and its use in Suzuki–Miyaura coupling could solve this problem (Scheme 1).

In our previous study to synthesize cyclopropane units (Figure 1), we obtained a trace of the nonracemic methylenecyclopropane derivative **3** in a magnesium-induced reductive desulfonylation of sulfonylated nonracemic cyclopropane derivative **2**. Considering the mechanism of this reaction to form **3**, the elimination of a hydroxyl group proceeded instead of protonation (Scheme 2a). Hence, to promote this elimination step with a much better leaving group, the hydroxyl group of **2** was mesylated and the product was subjected to the same reductive sulfonylation. As expected, **3** was successfully obtained in 88% yield (two steps).[8]

Scheme 2. Synthesis of the Nonracemic Methylenecyclopropane Unit 3 and Its Dibromination



The next step was the conversion of **3** to the bromomethylenecyclopropane derivative **1**. Dibromination of **3** by pyridinium tribromide and subsequent basic elimination of the resulting dibromide **4** was examined under several reaction conditions (Scheme 2b and Table 1).

The dibromide **4** was obtained as a 3:2 mixture of two diastereoisomers.[9] Through detailed experiments to examine the basic elimination of **4**, we found that a base/solvent combination of *t*-BuOK/THF was effective, where the yield was dramatically increased depending on the amount of *t*-BuOK used and the reaction temperature.[10] Treatment of **4** with *t*-BuOK (1.3 equiv) in THF at room temperature gave the desired **1** in 53% yield along with aldehydes **5** and **6**, which were probably produced through hydrolysis of **1**. However, when a solution of **4** and *t*-BuOK (1.3 equiv) in THF was stirred at −40 °C, **1** was obtained in 88% yield as an inseparable mixture of two stereoisomers: *E*:*Z* = 1:1.[11]

With the chiral bromomethylenecyclopropane **1** in hand, we examined the Suzuki–Miyaura coupling of **1** with 4-acetylphenylboronic acid (**7a**) by changing the Pd source and ligand. As shown in Table 2, when a solution of **1**, **7a** (1.3 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (10 mol %), and PPh_3 (20 mol %) in DMF was stirred at room temperature for 14 h, the expected coupling product **8a** was obtained in 43% yield (entry 1). With the PCy_3 ligand, the reaction proceeded more slowly (entry 2). With the $PdCl_2$(dppf) catalyst, **8a** was isolated in 53% yield (entry 7). Although we tried various kinds of bases and solvents, these conditions did not increase the yield of **8a**. Finally, using 1 equiv of Ag_2O[12] as an additive under $PdCl_2$(dppf) catalyst conditions, **8a** was successfully obtained in 85% yield (entry 8), probably due to an acceleration effect of Ag_2O on the transmetalation step in the Suzuki–Miyaura coupling reaction. Furthermore, the unsaturated bond of **8a** was stereoselectively reduced by general hydrogenation to give the desired nonracemic (*Z*)-cyclopropane derivative **9a**, in which the aromatic ring and (*Z*)-cyclopropane were connected by a C1 unit, methylene (Scheme 3).[13]

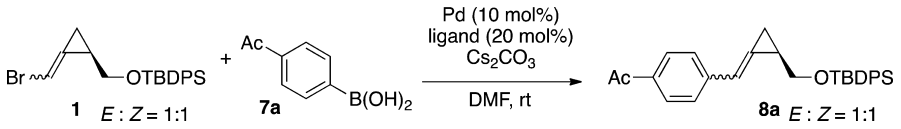
Experiments to probe the substrate scope of this Suzuki–Miyaura coupling are summarized in Table 3. The substituents on the boronic acid were not limited to phenyls. Sulfur- or nitrogen-containing heterocycles were also introduced into the methylenecyclopropane by this method in high to excellent yields (entries 5–9). Furthermore, not only boronic acid but also boronic acid pinacol ester worked (entries 3–9) much better at 40 °C in this reaction. We examined the reactions of **1** with some alkylboranes; however, they were unsuccessful. The *Z*-selective hydrogenation also proceeded in all substrates examined (Table 4).[14] Although a great number of organometallic catalyst induced ring-opening reactions of methylenecyclopropane have been reported,[15] our results indicate that the introduction of a bromo substituent at the terminal carbon

Table 1. Preparation of the Chiral Bromomethylenecyclopropane Unit 1

		isolated yield (%)			
entry	temp (°C)	**1**	**4** (SM)	**5**	**6**
1	room temp	53	17	15	3
2	0	70	11	10	3
3	−20	80	0	0	0
4	−40	88	0	0	0

dx.doi.org/10.1021/jo401675z | J. Org. Chem. 2013, 78, 11714–11720

Table 2. Optimization of Suzuki–Miyaura Coupling of 1 and 7



entry	Pd	ligand	additive (1 equiv)	time (h)	isolated yield of **8** (%)
1	$Pd(OAc)_2$	PPh_3		14	43
2	$Pd(OAc)_2$	PCy_3		72	46
3	$Pd(OAc)_2$	SPhos		24	complex mixture
4	$Pd(OAc)_2$	(±)-BINAP		24	NR
5	$Pd(dba)_2$	PPh_3		24	39
6	$Pd(dba)_2$	RuPhos		24	complex mixture
7		$PdCl_2(dppf)$		12	53
8		$PdCl_2(dppf)$	Ag_2O	7	85

Scheme 3. *cis*-Selective Hydrogenation of 8a to 9a

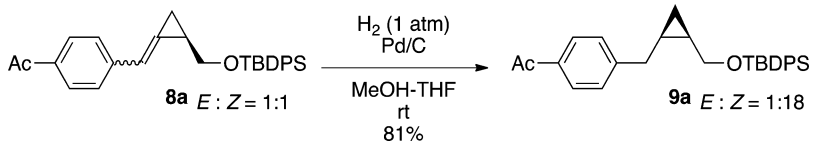
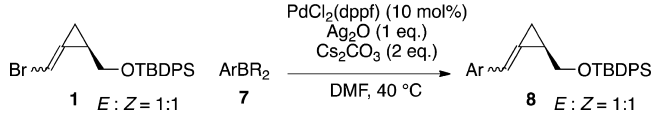
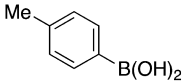
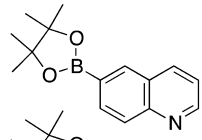
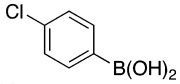
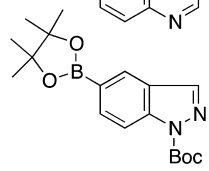
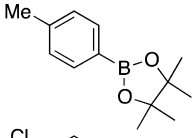
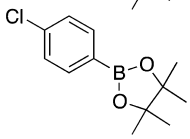
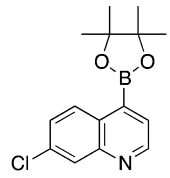
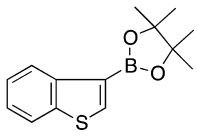
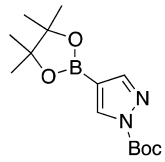


Table 3. Scope of Suzuki–Miyaura Coupling of 1 and 7



entry	$ArBR_2$	**8** (yield, %)	entry	$ArBR_2$	**8** (yield, %)
1		**8b** (69)	6		**8e** (96)
2		**8c** (72)	7		**8f** (89)
3		**8b** (91)			
4		**8c** (94)	8		**8g** (80)
5		**8d** (90)	9		**8h** (82)

of methylenecyclopropane was sufficient to provide a new entry for realizing the desired cross-coupling product.

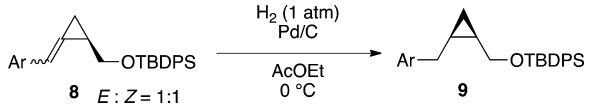
In conclusion, we established a novel preparative method of the chiral bromomethylenecyclopropane **1** and used it effectively in a Suzuki–Miyaura coupling reaction. The coupling products were stereoselectively converted to the corresponding (*Z*)-cyclopropane compounds, in which the aromatic ring and cyclopropane were connected by the C1 unit, methylene. This method should be useful for the synthesis of (*Z*)-cyclopropane-containing natural and/or unnatural compounds. Further medicinal chemical research based on this chemistry is ongoing in our laboratory.

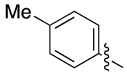
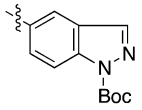
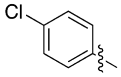
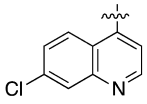
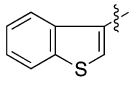
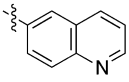
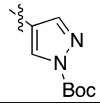
■ EXPERIMENTAL SECTION

General Considerations. ^1H NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 400 or 500 MHz, with TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 400 or 500 MHz. High-resolution mass spectroscopy (HRMS) was performed on an Orbitrap

dx.doi.org/10.1021/jo401675z | J. Org. Chem. 2013, 78, 11714–11720

Table 4. Stereoselective Hydrogenation of 8 to *cis*-Cyclopropane Derivative 9



entry	Ar	9 (yield, %)	E : Z [a]	entry	Ar	9 (yield, %)	E : Z [a]
1		**9b** (77)	1 : 16	5		**9f** (97)	1 : 17
2		**9c** (56)	1 : >20	6		**9g** (74)	1 : >20
3		**9d** (77)	1 : >20				
4		**9e** (92)	1 : 20	7		**9h** (89)	1 : >20

[a]Determined by ^{1}H NMR.

FT-MS spectrometer. Column chromatography was performed with silica gel 60N (spherical, nautral, 63−210 μm). Commercial solvents, including DMF, were used without further purification.

Synthesis and Reaction. *Preparation of Chiral Bromomethylenecyclopropane **1**. (R)-O-tert-Butyldiphenylsilyl-1-(methylenecyclopropyl)methanol (**3**).* To a solution of **2**[7a] (4.91 g, 10.2 mmol) in CH_2Cl_2 (80 mL) were added methanesulfonyl chloride (1.16 mL, 15.0 mmol) and triethylamine (2.09 mL, 15.0 mmol), and the mixture was stirred at room temperature for 10 h. To the mixture was added 1 M HCl, and the organic layer was extracted with $CHCl_3$, neutralized with saturated aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a crude residue. To a solution of the residue in MeOH (100 mL) was added Mg turnings (1.50 g, 62.5 mmol), and the mixture was stirred at 60 °C for 3 h. The mixture was poured into 0.5 M HCl at 0 °C, and the organic compounds were extracted with AcOEt, neutralized with $NaHCO_3$, washed with brine, dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt 49/1) to give **3** (2.88 g, 8.93 mmol, 88% for two steps) as a colorless oil: $[\alpha]_D^{17}$ = −23.5° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (1 H, m), 1.05 (9 H, s), 1.25 (1 H, m), 1.74 (1 H, m), 3.50 (1 H, dd, *J* = 10.6, 7.5 Hz), 3.70 (1 H, dd, *J* = 10.6, 6.1 Hz), 5.36 (1 H, m), 5.40 (1 H, m), 7.35−7.44 (6 H, m), 7.67−7.70 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 18.4, 19.7, 27.3, 66.8, 104.1, 127.9, 128.0, 129.0, 134.0, 134.3, 135.8, 135.9. LR-MS (EI) *m*/*z* 322 (M^+). Anal. Calcd for $C_{21}H_{26}OSi$: C, 78.21; H, 8.13. Found: C, 78.35; H, 8.20.

*1-Bromo-1-bromomethyl-2-(tert-Butyldiphenylsilyloxy)methylcyclopropane (**4**).* To a solution of **3** (250 mg, 0.775 mmol) in CH_2Cl_2 (6.0 mL) was added pyridinium tribromide (297 mg, 0.930 mmol) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. To the mixture was added saturated aqueous $Na_2S_2O_3$, and the organic layer was extracted with AcOEt, neutralized with saturated aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt 19/1) to give **4** (368 mg, 0.763 mmol, 98%, dr = 3/2) as a colorless oil: $[\alpha]_D^{27}$ = −11.4° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (1 H, m), 1.05 (9 H × 0.67, s), 1.07 (9 H, s), 1.11 (1 H × 0.67, m), 1.20 (1 H, m), 1.27 (1 H, m), 1.46 (1 H × 0.67, m), 1.98 (1 H × 0.67, m), 3.69 (2 H, s), 3.79 (1 H, dd, *J* = 10.8, 7.4 Hz), 3.71 (1 H × 0.67, dd, *J* = 11.4, 6.3 Hz), 3.88 (1 H, dd, *J* = 10.8, 5.7 Hz), 3.89 (2 H × 0.67, m), 3.98 (1 H × 0.67, dd, *J* = 11.4, 4.6 Hz), 7.37−7.46 (6 H + 6 H × 0.67, m), 7.63−7.71 (4 H + 4 H × 0.67, m); ^{13}C NMR (125 MHz, $CDCl_3$, diastereomeric mixture) δ 19.2, 19.2, 21.7, 22.1, 26.8, 28.9, 33.0, 36.2, 40.0, 41.6, 44.7, 60.9, 66.2, 127.7, 127.8, 129.7, 129.9, 129.9, 132.9, 133.0, 133.5, 133.7, 135.5, 135.6, 135.6; LR-MS (ESI) *m*/*z* 505 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{21}H_{26}Br_2NaOSi$ 503.0012, found 503.0016 [(M + Na)$^+$]. Anal. Calcd for $C_{21}H_{26}Br_2OSi$: C, 52.29; H, 5.43. Found: C, 52.03; H, 5.42.

*(R)-O-tert-Butyldiphenylsilyl-1-(bromomethylenecyclopropyl)-methanol (**1**).* A solution of **4** (48.2 mg, 0.100 mmol) in THF (900 μL) was cooled to −40 °C, and then *t*-BuOK (1 M THF solution, 130 μL, 0.130 mmol) was added and the mixture was stirred at −40 °C for 3 h. To the mixture was added saturated aqueous NH_4Cl, and the organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt 99/1) to give **1** (35.3 mg, 87.9 μmol, 88%, *E*/*Z* = 1/1) as a colorless oil: $[\alpha]_D^{21}$ = −50.3° (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (18 H, s), 1.09 (1 H, m), 1.24 (1 H, m), 1.40 (1 H, m), 1.48 (1 H, m), 1.91 (1 H, m), 2.04 (1 H, m), 3.53 (1 H, dd, *J* = 10.3, 6.9 Hz), 3.64 (2 H, m,), 3.96 (1 H, dd, *J* = 10.3, 5.2 Hz), 6.33 (1 H, s), 6.37 (1 H, s), 7.38−7.45 (12 H, m), 7.65−7.70 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 11.1, 13.4, 19.2, 19.2, 21.1, 24.4, 26.8, 63.6, 65.1, 95.3, 96.0, 127.7, 127.7, 129.6, 129.7, 130.3, 130.8, 133.6, 135.6, 135.6, 135.7; LR-MS (ESI) *m*/*z* 423 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{21}H_{25}BrNaOSi$ 423.0750, found 423.0757 [(M + Na)$^+$]. Anal. Calcd for $C_{21}H_{25}BrOSi$: C, 62.83; H, 6.28. Found: C, 62.94; H, 6.32.

*Preparation of ent-**1**. (S)-O-tert-Butyldiphenylsilyl-1-(methylenecyclopropyl)methanol (ent-**3**).* *ent*-**3** (3.97 g, 12.3 mmol, 86%) was prepared from *ent*-**2** (6.90 g, 14.4 mmol) as described for the preparation of compound **3**: $[\alpha]_D^{23}$ = 27.2° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}OSi$: C, 78.21; H, 8.13. Found: C, 78.36; H, 8.34.

*1-Bromo-1-bromomethyl-2-(tert-Butyldiphenylsilyloxy)methylcyclopropane (ent-**4**).* *ent*-**4** (566 mg, 1.17 mmol, 95%, dr =3/2) was prepared from *ent*-**3** (395 mg, 1.22 mmol) as described for the preparation of compound **4**: $[\alpha]_D^{25}$ = 11.1° (*c* 1.45, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}Br_2OSi$: C, 52.29; H, 5.43. Found: C, 52.48; H, 5.55.

*(S)-O-tert-Butyldiphenylsilyl-1-(bromomethylenecyclopropyl)-methanol (ent-**1**).* *ent*-**1** (38.1 mg, 94.9 μmol, 92%, *E*/*Z* = 1/1) was prepared from *ent*-**4** (49.6 mg, 0.103 mmol) as described for the preparation of compound **1**: $[\alpha]_D^{25}$ = 49.8° (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{21}H_{25}BrOSi$: C, 62.83; H, 6.28. Found: C, 62.96; H, 6.48.

*Suzuki−Miyaura Coupling of **1**: General Procedure.* To a solution of **1** in DMF (0.1 M) were added boronic acid (1.5 equiv), Cs_2CO_3 (2.0 equiv), Ag_2O (1.0 equiv), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol %), and the mixture was stirred at 40 °C for 2 h. The mixture was filtered

dx.doi.org/10.1021/jo401675z | J. Org. Chem. 2013, 78, 11714−11720

through Celite, and the filtrate was concentrated in vacuo. The residue was partitioned between Et_2O and water, washed with brine, dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt) to give the coupling product **8**.

Compound ***8a***. **8a** (37.5 mg, 85.1 μmol, 85%, colorless oil) was prepared from **1** (40.1 mg, 99.9 μmol) following the general procedure: $[\alpha]_D^{20}$ = −14.6° (*c* 1.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (19 H, s), 1.27 (1 H, m), 1.36 (1 H, m), 1.64 (1 H, m), 1.88 (1 H, m), 2.13 (1 H, m), 2.56 (3 H, s), 2.60 (3 H, s), 3.65 (1 H, dd, *J* = 10.8, 7.2 Hz), 3.72−3.84 (3 H, m), 6.78 (2 H, s), 7.26−7.93 (32 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 6.0, 9.7, 15.8, 19.0, 19.2, 19.3, 26.5, 26.6, 26.8, 26.8, 64.6, 65.6, 66.0, 118.2, 119.2, 126.6, 126.7, 127.6, 127.6, 127.7, 128.7, 128.7, 129.6, 129.6, 129.7, 130.9, 131.0, 133.3, 133.5, 133.7, 134.8, 135.2, 135.2, 135.3, 135.5, 135.5, 135.6, 135.6, 142.2, 142.6, 197.7; LR-MS (ESI) *m*/*z* 463 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{32}O_2NaSi$ 463.2064, found 463.2055 [(M + Na)$^+$].

Compound ***8b***. **8b** (37.4 mg, 90.6 μmol, 91%, colorless oil) was prepared from *rac*-**1** (40.0 mg, 99.6 μmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (1 H, m), 1.07 (18 H, s), 1.17 (1 H, m), 1.27 (1 H, m), 1.56 (1 H, m), 1.83 (1 H, m), 2.05 (1 H, m), 2.31 (3 H, s), 2.33 (3 H, s), 3.57 (1 H, dd, *J* = 10.8, 7.4 Hz), 3.61 (1 H, dd, *J* = 10.9, 6.9 Hz), 3.75 (1 H, dd, *J* = 10.8, 6.3 Hz), 3.91 (1 H, dd, *J* = 10.9, 5.7 Hz), 6.67 (1 H, m), 6.70 (1 H, m), 7.05 (2 H, d, *J* = 7.4 Hz), 7.11 (2 H, d, *J* = 8.0 Hz), 7.33−7.43 (16 H, m), 7.66−7.70 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 1.0, 6.1, 9.6, 15.6, 19.2, 19.2, 19.3, 21.2, 26.9, 66.0, 66.6, 118.6, 119.7, 125.5, 125.5, 126.6, 126.7, 127.6, 129.1, 129.2, 129.6, 133.6, 133.8, 133.9, 134.8, 135.6, 135.7, 136.5, 136.7; LR-MS (ESI) *m*/*z* 435 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{28}H_{32}ONaSi$ 435.2115, found 435.2114 [(M + Na)$^+$].

Compound ***8c***. **8c** (40.5 mg, 93.5 μmol, 94%, light yellow oil) was prepared from *rac*-**1** (40.2 mg, 0.100 mmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (1 H, m), 1.06 (18 H, s), 1.19 (1 H, m), 1.28 (1 H, m), 1.56 (1 H, m), 1.84 (1 H, m), 2.05 (1 H, m), 3.61 (1 H, dd, *J* = 10.8, 7.4 Hz), 3.71−3.80 (3 H, m), 6.67 (1 H, m), 6.68 (1 H, m), 7.19 (2 H, d, *J* = 8.0 Hz), 7.27 (2 H, d, *J* = 8.6 Hz), 7.33−7.48 (16 H, m), 7.64−7.70 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 5.9, 9.5, 15.7, 19.1, 19.2, 19.3, 26.8, 26.9, 65.8, 66.3, 117.7, 118.8, 127.6, 127.7, 127.8, 128.0, 128.6, 128.6, 129.7, 129.7, 132.3, 133.4, 133.6, 133.8, 135.6, 135.6, 136.1, 136.4; LR-MS (ESI) *m*/*z* 455 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{27}H_{29}OClNaSi$ 455.1568, found 455.1576 [(M + Na)$^+$].

Compound ***8d***. **8d** (40.6 mg, 89.3 μmol, 90%, light yellow oil) was prepared from *rac*-**1** (40.0 mg, 99.6 μmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (19 H, m), 1.21 (1 H, m), 1.40 (1 H, m), 1.59 (1 H, m), 1.97 (1 H, m), 2.07 (1 H, m), 3.67 (1 H, dd, *J* = 10.9, 6.9 Hz), 3.73−3.82 (3 H, m), 7.06 (2 H, m), 7.33−7.93 (30 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 6.8, 9.7, 17.2, 18.9, 19.2, 19.3, 26.9, 26.9, 66.2, 66.4, 111.1, 111.4, 121.2, 121.5, 121.8, 121.9, 122.8, 124.0, 124.1, 124.2, 124.3, 127.6, 127.7, 127.8, 127.9, 129.6, 128.6, 129.7, 129.7, 133.2, 133.5, 133.6, 133.8, 133.9, 133.9, 135.6 135.6, 137.9, 138.0, 140.2, 140.3; LR-MS (ESI) *m*/*z* 477 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{30}ONaSSi$ 477.1679, found 477.1683 [(M + Na)$^+$].

Compound ***8e***. **8e** (43.3 mg, 96.3 μmol, 96%, light yellow oil) was prepared from **1** (40.1 mg, 99.9 μmol) following the general procedure: $[\alpha]_D^{20}$ = −44.6° (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (19 H, m), 1.33 (1 H, m), 1.35 (1 H, m), 1.70 (1 H, m), 1.91 (1 H, m), 2.17 (1 H, m), 3.67 (1 H, dd, *J* = 10.8, 6.9 Hz), 3.77 (2 H, m), 3.90 (1 H, dd, *J* = 10.8, 5.7 Hz), 6.90 (2 H, m), 7.26−7.43 (14 H, m), 7.66−7.75 (10 H, m), 7.96−8.04 (4 H, m), 8.13 (2 H, m), 8.84 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 6.1, 9.7, 15.8, 19.2, 19.3, 19.3, 26.8, 26.8, 65.8, 66.3, 118.3, 119.3, 121.2, 121.3, 125.3, 125.5, 127.6, 128.1, 128.2, 128.5, 129.0, 129.0, 129.4, 129.5, 129.6, 129.6, 129.7, 133.4, 133.5, 133.8, 135.5, 135.6, 135.6, 135.6, 135.9, 136.0, 136.3, 147.6, 149.7, 149.8; LR-MS (ESI) *m*/*z* 450 [(M + H)$^+$]; HR-MS (ESI) calcd for $C_{30}H_{32}ONSi$ 450.2248, found 450.2246 [(M + H)$^+$].

Compound ***8f***. **8f** (48.0 mg, 89.1 μmol, 89%, colorless oil) was prepared from **1** (40.1 mg, 99.9 μmol) following the general procedure: $[\alpha]_D^{20}$ = −34.8° (*c* 1.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (1 H, m), 1.06 (9 H, s), 1.07 (9 H, s), 1.27 (1 H, m), 1.33 (1 H, m), 1.64 (1 H, m), 1.89 (1 H, m), 2.14 (1 H, m), 3.64 (1 H, dd, *J* = 10.8, 6.9 Hz), 3.75−3.80 (2 H, m), 3.84 (1 H, dd, *J* = 10.8, 6.3 Hz), 6.83 (2 H, m), 7.31−7.43 (12 H, m), 7.65−7.83 (12 H, m), 8.02−8.18 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 5.9, 9.6, 15.8, 19.2, 19.2, 26.8, 26.9, 28.2, 66.1, 66.3, 84.8, 84.8, 114.4, 114.5, 118.2, 118.6, 118.6, 119.3, 126.3, 126.9, 126.0, 127.6, 127.6, 127.9, 128.2, 129.6, 129.6, 129.6, 129.7, 133.4, 133.5, 133.6, 133.8, 134.0, 134.8, 135.5, 135.6, 135.6, 138.7, 138.7, 139.7, 139.8, 149.1, 149.1; LR-MS (ESI) *m*/*z* 561 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{33}H_{38}O_3N_2NaSi$ 561.2544, found 561.2546 [(M + Na)$^+$].

Compound ***8g***. **8g** (38.8 mg, 80.1 μmol, 80%, yellow oil) was prepared from **1** (40.2 mg, 0.100 mmol) following the general procedure.: $[\alpha]_D^{21}$ = −37.7° (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (9 H, s), 1.08 (9 H, s), 1.17 (1 H, m), 1.33 (1 H, m), 1.44 (1 H, m), 1.68 (1 H, m), 1.99 (1 H, m), 2.18 (1 H, m), 3.75−3.85 (4 H, m), 7.26−7.45 (14 H, m), 7.49 (1 H, m), 7.50 (1 H, m), 7.57−7.73 (9 H, m), 7.79 (1 H, d, *J* = 5.0 Hz), 8.03−8.14 (4 H, m), 8.70 (1 H, d, *J* = 5.0 Hz), 8.84 (1 H, d, *J* = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 6.2, 9.5, 16.4, 19.2, 19.3, 26.6, 26.8, 26.8, 65.0, 65.7, 112.9, 113.7, 117.5, 117.8, 124.4, 124.8, 124.8, 127.1, 127.7, 128.9, 129.6, 129.7, 129.7, 129.8, 133.2, 133.3, 133.6, 133.7, 134.8, 134.9, 135.0, 135.5, 135.5, 135.6, 135.6, 135.8, 135.9, 142.1, 142.5, 149.2, 149.2, 151.0, 151.3; LR-MS (ESI) *m*/*z* 484 [(M + H)$^+$]; HR-MS (ESI) calcd for $C_{30}H_{31}ONClSi$ 484.1858, found 484.1861 [(M + H)$^+$].

Compound ***8h***. **8h** (39.6 mg, 81.0 μmol, 82%, colorless oil) was prepared from **1** (39.9 mg, 99.4 μmol) following the general procedure: $[\alpha]_D^{20}$ = −45.3° (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (10 H, s), 1.06 (10 H, s), 1.34 (1 H, m), 1.46 (1 H, m), 1.63 (9 H, s), 1.65 (9 H, s), 1.89 (1 H, m), 1.96 (1 H, m), 3.52 (1 H, dd, *J* = 10.8, 7.4 Hz), 3.61 (1 H, dd, *J* = 10.8, 6.9 Hz), 3.71 (1 H, dd, *J* = 10.8, 6.3 Hz), 3.93 (1 H, dd, *J* = 10.8, 5.2 Hz), 6.54 (1 H, m), 6.56 (1 H, m), 7.34−7.44 (12 H, m), 7.64−7.72 (8 H, m), 7.84 (1 H, s), 7.85 (1 H, s), 7.96 (1 H, s), 8.01 (1 H, s); ^{13}C NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture) δ 7.4, 8.7, 17.2, 18.5, 19.2, 19.2, 26.8, 26.8, 27.9, 27.9, 65.4, 66.1, 85.2, 85.3, 108.1, 108.6, 123.1, 123.4, 126.3, 126.7, 127.6, 127.6, 127.6, 127.7, 127.7, 129.6, 129.6, 133.5, 133.6, 133.8, 134.8, 135.5, 135.6, 142.4, 142.6, 147.7, 147.7; LR-MS (ESI) *m*/*z* 511 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{36}O_3N_2NaSi$ 511.2387, found 511.2388 [(M + Na)$^+$].

Stereoselective Hydrogenation of ***8*** *to* ***9***: *General Procedure*. To a solution of **8** in AcOEt (0.1 M) was added 5% Pd/C (30 wt %), and the mixture was stirred at 0 °C for 15 min under Ar. The mixture was then stirred at the same temperature for 1 h under an H_2 atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt) or preparative TLC to give cyclopropane **9** as an inseparable diastereomeric mixture.

Compound ***9a***. To a solution of **8a** (29.1 mg, 66.0 μmol) in MeOH/THF (4/1, 660 μL) was added 5% Pd/C (9.0 mg), and the mixture was stirred at room temperature for 30 min under an H_2 atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give a crude residue, which was subjected to column chromatography (*n*-hexane/AcOEt 19/1) to give **9a** (23.8 mg, 53.8 μmol, 81%, diastereomixture, dr = 18/1) as a colorless oil: >99% ee by chiral HPLC (Chiralpak OD-H, hexane/*i*PrOH 99.5/0.5, 1.0 mL/min, 0 °C); $[\alpha]_D^{21}$ = +2.3° (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (1 H, m), 0.74 (1 H, m), 1.05 (9 H, s), 1.13 (1 H, m), 1.25 (1 H, m), 2.55 (1 H, m), 2.58 (3 H, s), 2.85 (1 H, dd, *J* = 15.4, 6.9 Hz), 3.60 (1 H, dd, *J* = 11.3, 8.6 Hz), 3.89 (1 H, dd, *J* = 11.3, 5.7 Hz), 7.36−7.44 (8 H, m), 7.66−7.69 (4 H, m), 7.86−7.88 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1, 16.5, 18.3, 19.2, 26.5, 26.9, 34.3, 63.9, 127.6, 127.7, 128.4, 128.5, 129.6, 129.6, 133.9, 134.8, 135.0, 135.2, 135.6, 135.6, 148.3, 198.0; LR-MS (ESI) *m*/*z* 465 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{34}O_2NaSi$ 465.2220, found 465.2215 [(M

+ Na)$^+$]. Anal. Calcd for $C_{29}H_{34}O_2Si\cdot0.3H_2O$: C, 77.74; H, 7.78. Found: C, 77.82; H, 7.78.

Compound ***9b***. **9b** (23.1 mg, 55.7 μmol, 77%, dr = 16/1, white oil) was prepared from **8b** (30.0 mg, 72.7 μmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (1 H, m), 0.70 (1 H, m), 1.06 (9 H, s), 1.11 (1 H, m), 1.20 (1 H, m), 2.31 (3 H, s), 2.41 (1 H, dd, *J* = 14.8, 8.0 Hz), 2.79 (1 H, dd, *J* = 14.8, 6.3 Hz), 3.65 (1 H, dd, *J* = 10.8, 8.0 Hz), 3.85 (1 H, dd, *J* = 10.8, 5.7 Hz), 7.08 (2 H, d, *J* = 8.0 Hz), 7.16 (2 H, d, *J* = 8.0 Hz), 7.36−7.44 (6 H, m), 7.65−7.71 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4, 17.2, 18.3, 19.2, 21.0, 26.9, 33.9, 64.2, 127.6, 128.2, 128.9, 129.5, 134.0, 134.1, 135.1, 135.6, 135.7, 139.4; LR-MS (ESI) *m*/*z* 437 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{28}H_{34}ONaSi$ 437.2271, found 437.2272 [(M + Na)$^+$]. Anal. Calcd for $C_{28}H_{34}OSi\cdot0.05CHCl_3$: C, 80.10; H, 8.16. Found: C, 80.07; H, 8.34.

Compound ***9c***. **9c** (18.9 mg, 43.4 μmol, 56%, dr = >20/1, white oil) was prepared from **8c** (33.6 mg, 77.6 μmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (1 H, m), 0.71 (1 H, m), 1.06 (9 H, s), 1.08 (1 H, m), 1.22 (1 H, m), 2.46 (1 H, dd, *J* = 14.8, 8.0 Hz), 2.76 (1 H, dd, *J* = 14.8, 6.3 Hz), 3.60 (1 H, dd, *J* = 11.4, 8.6 Hz), 3.87 (1 H, dd, *J* = 11.4, 5.7 Hz), 7.20−7.23 (4 H, m), 7.36−7.44 (6 H, m), 7.64−7.69 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1, 16.8, 18.3, 19.2, 26.9, 33.6, 63.9, 127.6, 127.6, 128.3, 129.6, 129.7, 131.4, 133.9, 133.9, 135.6, 135.6, 140.9; LR-MS (ESI) *m*/*z* 457 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{27}H_{31}OClNaSi$ 457.1725, found 457.1729 [(M + Na)$^+$]. Anal. Calcd for $C_{27}H_{31}ClOSi$: C, 74.54; H, 7.18. Found: C, 74.66; H, 7.45.

Compound ***9d***. **9d** (27.1 mg, 59.3 μmol, 77%, dr = >20/1, colorless oil) was prepared from **8d** (34.9 mg, 76.8 μmol) following the general procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (1 H, m), 0.80 (1 H, m), 1.06 (9 H, s), 1.29 (2 H, m), 2.72 (1 H, dd, *J* = 16.5, 6.9 Hz), 2.96 (1 H, dd, *J* = 16.5, 5.7 Hz), 3.64 (1 H, dd, *J* = 11.3, 8.0 Hz), 3.90 (1 H, dd, *J* = 11.3, 5.2 Hz), 7.26 (1 H, s), 7.30−7.43 (8 H, m), 7.63−7.70 (5 H, m), 7.85 (1 H, d, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4, 15.0, 18.2, 19.2, 26.9, 27.4, 64.0, 121.3, 121.6, 122.8, 123.7, 124.1, 127.6, 129.5, 133.9, 133.9, 135.6, 135.6, 136.9, 139.1, 140.4; LR-MS (ESI) *m*/*z* 479 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{32}ONaSSi$ 479.1835, found 479.1843 [(M + Na)$^+$]. Anal. Calcd for $C_{29}H_{32}OSSi\cdot0.1H_2O$: C, 75.97; H, 7.08. Found: C, 75.81; H, 7.28.

Compound ***9e***. **9e** (40.0 mg, 88.6 μmol, 92%, dr = 20/1, colorless oil) was prepared from **8e** (43.3 mg, 96.3 μmol) following the general procedure: >99% ee by chiral HPLC (Chiralpak OD-H, hexane/*i*PrOH 99.5/0.5, 1.0 mL/min, 0 °C); $[\alpha]_D^{19}$ = +0.4° (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (1 H, m), 0.78 (1 H, m), 1.05 (9 H, s), 1.16−1.33(2 H, m), 2.70 (1 H, dd, *J* = 14.8, 7.4 Hz), 2.99 (1 H, dd, *J* = 14.8, 6.3 Hz), 3.65 (1 H, dd, *J* = 10.8, 8.0 Hz), 3.93 (1 H, dd, *J* = 10.8, 5.2 Hz), 7.34−7.44 (7 H, m), 7.63−7.70 (6 H, m), 8.02 (1 H, d, *J* = 8.0 Hz), 8.07 (1 H, d, *J* = 8.0 Hz), 8.85 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.2, 16.7, 18.3, 19.2, 26.9, 34.2, 64.0, 121.0, 125.9, 127.6, 128.3, 129.1, 129.6, 131.1, 133.9, 133.9, 135.6, 135.6, 140.9, 147.2, 149.6; LR-MS (ESI) *m*/*z* 452 [(M + H)$^+$]; HR-MS (ESI) calcd for $C_{30}H_{34}ONSi$ 452.2404, found 452.2394 [(M + H)$^+$]. Anal. Calcd for $C_{30}H_{33}ONSi\cdot0.1H_2O$: C, 79.46; H, 7.38; N, 3.09. Found: C, 79.44; H, 7.61; N, 3.06.

Compound ***9f***. **9f** (46.7 mg, 86.4 μmol, 97%, dr = 17/1, colorless oil) was prepared from **8f** (48.0 mg, 89.1 μmol) following the general procedure: $[\alpha]_D^{19}$ = −1.1° (*c* 0.87, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (1 H, m), 0.74 (1 H, m), 1.06 (9 H, s), 1.16 (1 H, m), 1.27 (1 H, m), 1.73 (9 H, s), 2.65 (1 H, dd, *J* = 15.4, 7.4 Hz), 2.91 (1 H, dd, *J* = 15.4, 6.9 Hz), 3.63 (1 H, dd, *J* = 10.8, 8.6 Hz), 3.91 (1 H, dd, *J* = 10.8, 5.2 Hz), 7.35−7.48 (7 H, m), 7.65−7.70 (5 H, m), 8.04−8.08 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.0, 17.1, 18.4, 19.2, 26.9, 28.2, 33.9, 63.9, 84.6, 114.2, 119.8, 126.2, 127.6, 129.6, 130.1, 133.9, 133.9, 135.6, 135.6, 138.1, 138.3, 139.5, 149.3; LR-MS (ESI) *m*/*z* 563 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{33}H_{40}O_3N_2NaSi$ 563.2700, found 563.2686 [(M + Na)$^+$]. Anal. Calcd for $C_{33}H_{40}O_3N_2Si\cdot1.0H_2O$: C, 70.93; H, 7.58; N, 5.01. Found: C, 70.80; H, 7.47; N, 5.03.

Compound ***9g***. **9g** (28.8 mg, 59.2 μmol, 74%, dr = >20/1, colorless oil) was prepared from **8g** (38.8 mg, 80.1 μmol) following the general procedure: $[\alpha]_D^{20}$ = +3.7° (*c* 0.94, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (1 H, m), 0.82 (1 H, m), 1.04 (9 H, s), 1.25 (1 H, m), 1.36 (1 H, m), 2.94 (1 H, dd, *J* = 16.0, 7.4 Hz), 3.23 (1 H, dd, *J* = 16.0, 6.3 Hz), 3.60 (1 H, dd, *J* = 11.4, 8.6 Hz), 3.97 (1 H, dd, *J* = 11.4, 5.7 Hz), 7.31−7.50 (8 H, m), 7.62−7.66 (4 H, m), 7.91 (1 H, m), 8.10 (1 H, m), 8.79 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.3, 14.9, 18.4, 19.2, 26.8, 30.2, 63.7, 120.6, 124.9, 126.1, 127.1, 127.6, 129.0, 129.6, 133.7, 134.7, 135.5, 135.6, 148.3, 148.6, 151.5; LR-MS (ESI) *m*/*z* 508 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{30}H_{32}ONClNaSi$ 508.1834, found 508.1841 [(M + Na)$^+$]. Anal. Calcd for $C_{30}H_{32}ONClSi\cdot0.2H_2O$: C, 73.58; H, 6.67; N, 2.86. Found: C, 73.62; H, 6.81; N, 2.90.

Compound ***9h***. **9h** (35.3 mg, 71.9 μmol, 89%, dr = >20/1, colorless oil) was prepared from **8h** (39.6 mg, 81.0 μmol) following the general procedure: $[\alpha]_D^{22}$ = +1.7° (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (1 H, m), 0.72 (1 H, m), 1.04 (9 H, s), 1.08 (1 H, m), 1.21 (1 H, m), 1.64 (9 H, s), 2.32 (1 H, dd, *J* = 16.0, 8.6 Hz), 2.61 (1 H, dd, *J* = 16.0, 6.3 Hz), 3.57 (1 H, dd, *J* = 11.4, 8.6 Hz), 3.85 (1 H, dd, *J* = 11.4, 5.7 Hz), 7.36−7.44 (6 H, m), 7.60 (1 H, s), 7.65−7.69 (4 H, m), 7.90 (1 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1, 16.1, 18.1, 19.2, 23.0, 26.8, 27.9, 63.8, 84.9, 124.8, 127.6, 127.9, 129.6, 133.9, 133.9, 135.6, 135.6, 144.4, 147.8; LR-MS (ESI) *m*/*z* 513 [(M + Na)$^+$]; HR-MS (ESI) calcd for $C_{29}H_{38}O_3N_2NaSi$ 513.2544, found 513.2530 [(M + Na)$^+$]. Anal. Calcd for $C_{29}H_{38}O_3N_2Si\cdot0.1H_2O$: C, 70.72; H, 7.82; N, 5.69. Found: C, 70.61; H, 7.92; N, 5.63.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for M.A.: arisawa@phs.osaka-u.ac.jp.

*E-mail for S.S.: shu@pharm.hokudai.ac.jp.

Present Address

§Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research (21390028 to S.S. and 2310550201 and 2179000300 to M.A.) from the Japan Society for the Promotion of Science. This work was also supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (MEXT), ACT-C from the Japan Science and Technology Agency (JST), and Takeda Science Foundation.

■ REFERENCES

(1) (a) de Meijere, A.; Kozhushkov, S. I.; Schill, H. *Chem. Rev.* **2006**, *106*, 4926−4996. (b) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575−608.

(2) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538−4583.

(3) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589−8627. (c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625−1648. (d) Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 971−973. (e) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247−1270. (f) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477−501. (g) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (h) de Meijere, A.; Kozhushkov, S. I.; Had-Jiarapoglou, L. P. *Top. Curr. Chem.* **2000**, *207*, 149−227.

(i) Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett.* **2006**, *8*, 2671−2673. (j) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041−7095.

(4) (a) Clemons, P. A.; Bodycombe, N. E.; Carrinski, H. A.; Wilson, J. A.; Shamji, A. F.; Wagner, B. K.; Koehler, A. N.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 18787−18792. (b) DeLorbe, J. E.; Clements, J. H.; Teresk, M. G.; Benfield, A. P.; Plake, H. R.; Millspaugh, L. E.; Martin, S. F. *J. Am. Chem. Soc.* **2009**, *131*, 16758−16770. (c) Benfield, A. P.; Teresk, M. G.; Plake, H. R.; DeLorbe, J. E.; Millspaugh, L. E.; Martin, S. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6830−6835. (d) Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 205−215.

(5) (a) Abramovitch, A.; Fensterbank, L.; Malacria, M.; Marek, I. *Angew. Chem., Int. Ed.* **2008**, *47*, 6865−6868. (b) Preparation of trans-type compounds has been reported. Chen, H.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, , 1609−1613.

(6) (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111−129. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213−1270. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117−3179. (d) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409−3412. (e) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060−5061.

(7) For example: (a) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669−1677. (b) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980−1988. (c) Watanabe, M.; Kazuta, Y.; Hayashi, H.; Yamada, S.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2006**, *49*, 5587−5596. (d) Watanabe, M.; Hirokawa, T.; Kobayashi, T.; Yoshida, A.; Ito, Y.; Yamada, S.; Orimoto, N.; Yamasaki, Y.; Arisawa, M.; Shuto, S. *J. Med. Chem.* **2010**, *53*, 3585−3593.

(8) This preparative method for nonracemic methylenecyclopropane is unique. For conventional methods, see: (a) Achmatowicz, B.; Kabat, M. M.; Krajewski, J.; Wicha, J. *Tetrahedron* **1992**, *48*, 10201−10210. (b) Baldwin, J. E.; Adlington, R. M.; Bebbington, D.; Russell, A. T. *Tetrahedron* **1994**, *50*, 12015−12028. (c) Chen, X.; Zemlicka, J. *J. Org. Chem.* **2002**, *67*, 286−289.

(9) The stereochemistries of the major and minor isomers were not determined.

(10) When DBU or KOH was used as a base, no reaction proceeded or the TBDPS group on the hydroxyl group was cleaved.

(11) When crude **4** was used without purification by column chromatography, **1** was obtained from **3** in 82% yield (two steps). The preparation of *ent*-**1** from (*S*)-epichlorohydrin can be carried out in the same manner; see the Experimental Section.

(12) A previous example using Ag_2O as an effective additive in Suzuki−Miyaura coupling; Uenichi, J.; Beau, J.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756−4758.

(13) The relative stereochemistry of **9a** was determined by NOE experiments in $CDCl_3$: see the Supporting Information.

(14) In some cases, a trace of cyclopropane ring-opening byproduct was obtained under these conditions.

(15) Reviews: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117−3179.