



Asymmetric reduction of aliphatic ketones and acyl silanes using chiral *anti*-pentane-2,4-diol and a catalytic amount of 2,4-dinitrobenzenesulfonic acid

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ARTICLE INFO

Article history:

Received 10 May 2010

Received in revised form 3 June 2010

Accepted 4 June 2010

Available online 10 June 2010

Keywords:

Asymmetric reduction

Ketone

Acyl silane

Meerwein–Ponndorf–Verley reduction

Oppenauer oxidation

ABSTRACT

Aliphatic ketones were reduced to the corresponding secondary alcohols by using *anti*-1,3-diol and a catalytic amount of 2,4-dinitrobenzenesulfonic acid (DNBSA) in benzene at reflux. Addition of 1-octanethiol in that media improved the efficiency of the reduction. Asymmetric reduction of aliphatic ketones was performed by using chiral *anti*-pentane-2,4-diol, and highly asymmetric induction (up to >99% ee) was observed in the reduction of *tert*-alkyl ketones. Asymmetric reduction of acyl silanes using chiral *anti*-pentane-2,4-diol and DNBSA proceeded efficiently in the absence of octanethiol and the corresponding α -silyl alcohols were obtained in high yields with high ees.

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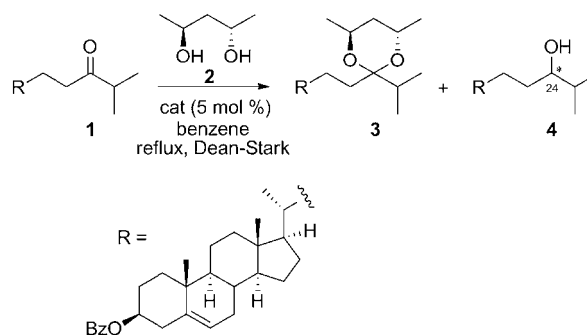
1. Introduction

Meerwein–Ponndorf–Verley (MPV) reduction of ketone has distinguishing usefulness in organic synthesis.¹ A stoichiometric amount of metal alkoxides (usually aluminum triisopropoxide) is usually employed as a reducing agent, and the metal part plays an important role in the MPV reduction: it activates the carbonyl group of ketones to be reduced and promotes hydride transfer from the C–H bond of the alkoxide. Though extensive efforts have been made to develop a catalytic method of MPV reduction,^{2,3} there had been no report of metal-free MPV reduction of ketone with alcohol until our previous brief report.⁴ We report here details of asymmetric reduction of ketones and acyl silanes that uses chiral *anti*-pentane-2,4-diol and a catalytic amount of a strong Brønsted acid.

In the course of our study on stereoselective reduction of 24-oxocholesterol derivatives,⁵ we planned aluminum hydride-promoted ring cleavage of chiral acetal **3**.⁶ We attempted to prepare chiral acetal **3** from ketone **1** and chiral diol **2** by using a catalytic amount (5 mol %) of pyridinium *p*-toluenesulfonate (PPTS) in benzene at reflux with continuous removal of water (Table 1). However, the desired acetal **3** was obtained in only 8% yield, probably due to steric hindrance around the carbonyl group of ketone **1** (entry 1).⁷ The use of *p*-toluenesulfonic acid (TsOH) instead of PPTS gave acetal **3** also in low (12%) yield, but alcohol **4** was surprisingly obtained in 4% yield (entry 2). When

Table 1

Brønsted acid-controlled selectivity between acetalization and reduction of ketone **1** with diol **2**



Entry	Catalyst	Time (h)	3 (% yield ^a)	4 (% yield ^a)
1	PPTS	34	8	0
2	TsOH	6	12	4
3	DNBSA ^b	2	0	23 ^c

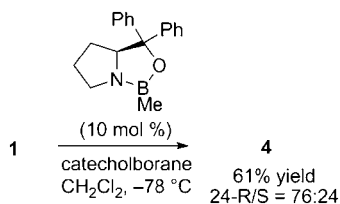
^a Isolated yield.

^b 2,4-Dinitrobenzenesulfonic acid.

^c 24-*R/S*=88.5:11.5.

2,4-dinitrobenzenesulfonic acid (DNBSA), a stronger Brønsted acid than TsOH, was employed, acetal **3** was not formed at all, but alcohol **4** was obtained in 23% yield (entry 3). Moreover, stereoselectivity for this reduction (24-*R/S*=88.5:11.5) was higher than that for Corey–Shibata–Bakshi (CBS) reduction⁸ (24-*R/S*=76:24,⁵ Scheme 1).

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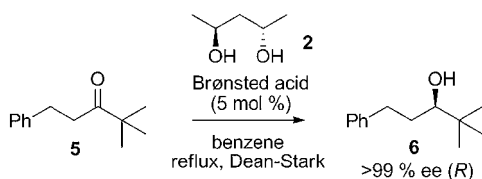
Scheme 1. CBS reduction of **1**.

2. Results and discussion

2.1. Asymmetric reduction of ketones

Various Brønsted acids were further tested for the reaction of ketone **5** with chiral diol **2** in order to find an appropriate Brønsted acid catalyst for the reduction of ketones (Table 2). In reduction of *tert*-butyl ketone **5**, trifluoroacetic acid (TFA) and TsOH did not work as catalysts (entries 1 and 2), though the use of TsOH gave alcohol **6** in the reduction of isopropyl ketone **1** (Table 1, entry 2). The steric hindrance of *tert*-butyl ketone **5** retarded the reduction with **2**. The use of stronger Brønsted acids such as 2-fluorobenzenesulfonic acid (FBSA)⁹ and 4-nitrobenzenesulfonic acid (NBSA)¹⁰ gave alcohol **6** in 4% and 3% yields, respectively, while the use of 2,4-dinitrobenzenesulfonic acid (DNBSA)¹¹ and trifluoromethanesulfonic acid (TfOH) gave alcohol **6** in 13% and 11% yields, respectively (entries 3–5 and 7). Thus, a strong Brønsted acid worked as an effective catalyst for the present reduction, and DNBSA was found to be an appropriate Brønsted acid catalyst. Increasing the amount of DNBSA from 5 to 20 mol % resulted in rapid disappearance of diol **2** and lowered the yield of **6**, probably because acid-catalyzed dehydration of **6** took place (entry 6). Acetalization of *tert*-butyl ketone **5** with diol **2** was not observed with any of the Brønsted acids shown in Table 2. In all of the cases described above, optical purity of the reduction product **6** was >99% ee (*R*), and the enantioselectivity did not depend on the Brønsted acid employed.

Table 2
Effects of Brønsted acids in reduction of ketone **5** to alcohol **6** with diol **2**



Entry	Brønsted acid ^a	Time (h)	Isolated yield (%)
1	TFA	2	0
2	TsOH	18	Trace
3	FBSA	5.5	4
4	NBSA	4	3
5	DNBSA	4	13
6 ^b	DNBSA	1.5	6
7	TfOH	2	11

^a TFA: trifluoroacetic acid; TsOH: *p*-toluenesulfonic acid; FBSA: 2-fluorobenzenesulfonic acid; NBSA: 4-nitrobenzenesulfonic acid; DNBSA: 2,4-dinitrobenzenesulfonic acid; TfOH: trifluoromethanesulfonic acid.

^b DNBSA (20 mol %) was used.

Next, the reduction of ketone **5** with diol **2** was carried out in various solvents at reflux (Table 3). The reduction of **5** in toluene gave alcohol **6** in 4% yield (entry 2), and the use of halogenated hydrocarbons such as carbon tetrachloride and dichloroethane gave alcohol **6** in low yields (entries 3 and 4). Reduction in other polar solvents such as THF, diisopropyl ether, ethanol, and acetonitrile did not give **6**. Therefore, benzene was found to be the most suitable solvent for the present reduction.

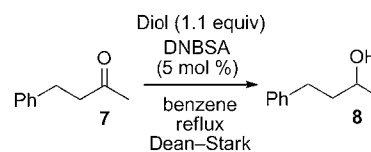
Table 3
Effects of solvents in reduction of ketone **5** to alcohol **6** with diol **2**^a

Entry	Solvent	Time (h)	Isolated yield (%)
1	Benzene	4	13
2	Toluene	1	4
3	CCl ₄	5	5
4	ClCH ₂ CH ₂ Cl	1	9

^a Ketone **5** (1.0 equiv), diol **2** (1.1 equiv), and DNBSA (5 mol %) were used. Reactions were carried out at reflux. In all cases, optical purity of **6** was >99% ee, which was determined by chiral HPLC.

Various diols were employed in reduction of methyl ketone **7** to alcohol **8** in order to clarify what structural feature of diol was required for the DNBSA-reduction of ketone (Table 4). The effect of methyl groups of diol **2** was first examined by using (3*R*)-butan-1,3-

Table 4
Effects of diols in DNBSA-catalyzed reduction of ketone **7** to alcohol **8** in benzene at reflux



Entry	Diol	Time (h)	8 (% Yield) ^a
1		3	27 ^b
2		2	4 ^c
3		2	9
4		2	Trace ^d
5		0.5	Trace ^e
6		2	0
7		2	0 ^f
8		2	41
	15a: R=Et		
9	15b: R= <i>i</i> -Pr	2	46
10	15c: R= <i>t</i> -Bu	3	18
11	15d: R= <i>i</i> -Bu	1	28 ^g
12	15e: R=Ph	1.5	Trace

^a Isolated yield.

^b 48% ee (*R*).

^c ee was not determined.

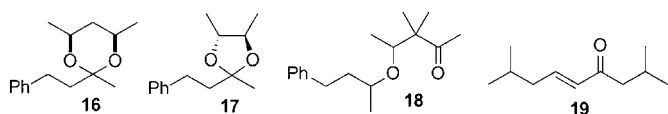
^d Compound **16** was isolated in 55% yield (dr=61:39).

^e Compound **17** was isolated in 56% yield.

^f Compound **18** was isolated in 32% yield.

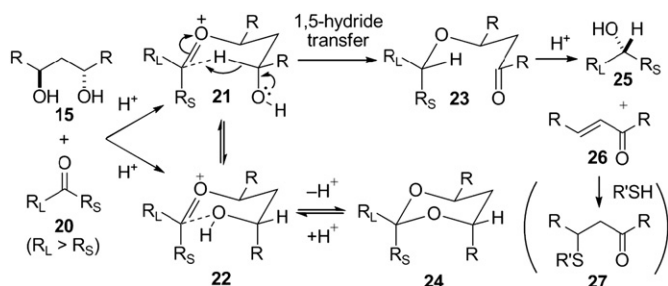
^g Compound **19** was isolated in 18% yield (based on **7**).

diol (**9**) and propane-1,3-diol (**10**). It was found that lack of the methyl substituent of **2** significantly decreased the yield of reduction product **8** from 27% to 4–9% (entries 1–3). It was noted that even diol **10** reduced ketone **7** by the catalysis of DNBSA. With regard to the stereochemistry of 1,3-diol, *anti*-configuration was critical for the present reduction because *syn*-1,3-diol **11** gave the reduction product **8** in a trace amount but gave acetal **16** in 55% yield (entry 4). Also, the use of *anti*-1,2-diol **12** and *anti*-1,4-diol **13** did not give reduction product **8**, suggesting that the two hydroxy groups of diol had to be positioned at the 1,3-position (entries 5 and 6). Therefore, *anti*-1,3-diol structure was found to be required for effective reduction of ketone. The use of (\pm)-*anti*-diol **14**, which did not have any hydrogens at its 3-position, did not give reduction product **8** but afforded β -alkoxy ketone **18** in 32% yield (entry 7).



anti-1,3-Diols (\pm)-**15a–e** having various substituents at their 1,3-position were next employed. It was found that as the steric bulkiness increased from methyl to isopropyl groups, the yield of alcohol **8** increased, whereas substitution with a *tert*-butyl group decreased the yield of **8** (entries 8–10). The use of diol **15d** (R=*i*-Bu) resulted in rapid disappearance of **15d** and the yield of **8** was not improved compared to that in the case of diol **2**. In this case, enone **19** was isolated in 18% yield (entry 11). A diol having a phenyl group (**15e**) did not catalyze the reduction of **7**. Before reduction of **7**, dehydration of benzylic alcohol **15e** might proceed under acidic conditions (entry 12).

A plausible mechanism for reduction of ketone **20** with diol **15** by catalysis with DNBSA is shown in Scheme 2. Ketone **20** reacts with *anti*-1,3-diol **15** in the presence of Brønsted acid to give oxocarbenium ion (**21** or **22**). Acetal **24** can be formed via oxocarbenium ion **22**,¹² but DNBSA, a strong Brønsted acid, catalyzes stereoselective cleavage¹³ of the acetal ring of **24** to regenerate oxocarbenium ion **22**. Oxocarbenium ion **21**, which has two R groups in equatorial positions, is formed by C–C bond rotation in oxocarbenium ion **22**. Then, 1,5-hydride transfer¹⁴ proceeds via a six-membered transition state shown in **21** to form β -alkoxy ketone **23**. Thus, intramolecular MPV reduction and Oppenauer oxidation¹⁵ proceed in this step. Alcohol **25** and enone **26** are formed from **23** by Brønsted acid-catalyzed elimination. The involvement of β -alkoxy ketone **23** and enone **26** was confirmed by isolation of compounds **18** and **19**, respectively.



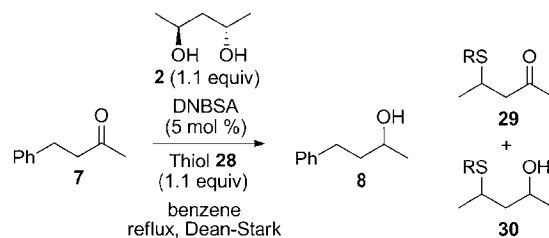
Scheme 2. Plausible mechanism for DNBSA-catalyzed reduction of ketone **20** to alcohol **25** using *anti*-1,3-diol **15**.

Competitive reduction of enone **26** with diol **15** was thought to be the main reason for the low efficiency in DNBSA-catalyzed reduction of ketone **20** with diol **15**.¹⁶ The improved efficiency in the reduction with diol **15b** (R=*i*-Pr) was attributed to slow reduction of sterically demanding enone **26b** (R=*i*-Pr). It was then expected that addition of thiol to enone **26** would give **27**, which was less reactive for the reduction with diol **15** compared with enone **26**.

Various thiols **28a–e** were used for DNBSA-catalyzed reduction of ketone **7** with diol **2** in order to improve the efficiency of the reduction (Table 5). It was found that addition of aromatic thiols, such as benzenethiol **28a**, *o*-methylbenzenethiol **28b**, and *p*-methoxybenzenethiol **28c** improved the yield of alcohol **8** (entries 2–4). Further improvement was observed when aliphatic thiols were used: octanethiol **28d** and 2-ethylhexanethiol **28e** gave alcohol **8** in 62% and 61% yields, respectively (entries 5 and 6). Increasing the amount of diol **2** from 1.1 to 2.0 equiv did not change the efficiency of the reduction (compare entry 5 with entry 7.). β -Arylthio or β -alkylthio pentan-2-ones **29a–e**, which were formed by conjugate addition of thiol to in situ-formed enone, were isolated in all cases. However, alcohols **30a–e**, which were formed by reduction of **29a–e** with diol **2**, were also obtained. These results suggested that DNBSA-catalyzed reduction of ketone **7** with diol **2** was improved by adding octanethiol, but consumption of diol **2**, which resulted from competitive reduction of ketone **29**, was not inhibited.

Table 5

Effects of thiols **28a–e** in DNBSA-catalyzed reduction of ketone **7** to alcohol **8** in benzene at reflux



Entry	Thiol	28	Time (h)	8 ^a	29 ^a	30 ^a
1	None		3	27	—	—
2	PhSH	28a	3	40	18	5
3	<i>o</i> -MeC ₆ H ₄ SH	28b	2.5	50	44	9
4	<i>p</i> -MeOC ₆ H ₄ SH	28c	2.5	50	56	12
5	C ₈ H ₁₇ SH	28d	3.5	62	55	16
6	BuCH ₂ EtCH ₂ SH	28e	2.5	61	55	15
7 ^b	C ₈ H ₁₇ SH	28d	3	62	61	24

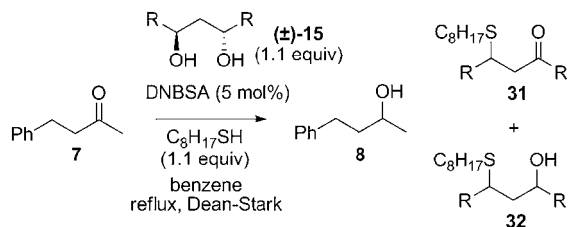
^a Isolated yield (%) based on **7**.

^b Two equivalents of diol **2** were employed.

Effects of substituents of diol **15** bearing ethyl, propyl, isopropyl, and isobutyl groups as the R group in the reduction of ketone **7** were investigated again in the presence of octanethiol (Table 6). Compared with diol **2**, the use of **15a** (R=Et) and **15b** (R=*i*-Pr) did not improve the yield of alcohol **8** (entries 1, 2, and 4), though diols **15a** and **15b** clearly improved the efficiency of the reduction in the absence of octanethiol (Table 4, entries 8 and 9). When sterically hindered diol **15b** was

Table 6

Effects of diol **15** in DNBSA-catalyzed reduction of ketone **7** to alcohol **8** in the presence of octanethiol



Entry	Diol (R)	Time (h)	8 ^a	31 ^a	32 ^a
1	2 (Me)	3.5	62	55	16
2	15a (Et)	1.5	64	52	7
3	15f (<i>n</i> -Pr)	1.5	62	52	6
4	15b (<i>i</i> -Pr)	1	50	32	0
5	15d (<i>i</i> -Bu)	2	54	29	0

^a Isolated yield (%) based on **7**.

employed, the addition of octanethiol to in situ-formed enone took place slowly to afford the corresponding β -octylthio ketone **31b** in 32% yield, which was lower than that in the case of diol **2** (55%) (entries 1 and 4). Insufficient trapping of enone with octanethiol might cause the undesired reduction of enone with diol, which was the reason why further improvement was not observed when sterically demanding diols were employed in the presence of octanethiol. Therefore, the combination of octanethiol and diol **2**, which is commercially available as a chiral compound, was employed in the following experiments as optimized conditions.

The scope and limitations of DNBSA-catalyzed asymmetric reduction of ketones **33** with chiral diol **2** were investigated by using octanethiol as an additive (Table 7). Reduction of *tert*-alkyl ketones such as **33a,b** and **5** proceeded with high asymmetric induction (99>99% ee) in 18–36% yields (entries 1–3). Reduction of *sec*-alkyl methyl ketones **31c–f** proceeded to give the corresponding alcohols **34c–f** in 42–57% yields with 82–93% ees (entries 4–7), while reduction of isopropyl ketones **33g** and **1** proceeded in low yields with moderate selectivities (entries 8 and 9). The steric hindrance around the carbonyl group of **33g** and **1**, which was increased by substitution with a longer alkyl chain than the methyl group of **33c–f**, was the reason for the low yields of **34g** and **4**. Reduction of *n*-alkyl methyl ketones **33h–j** proceeded in 50–64% yields and with about 50% ees (entries 10–12). In reduction of aromatic ketone, acetophenone **33k** did not give the desired alcohol **34k** (entry 13). Detection of styrene by TLC analysis suggested that dehydration of the formed benzylic alcohol **34k** with DNBSA took place.

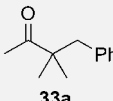
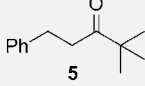
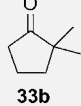
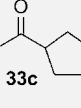
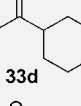
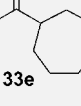
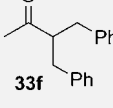
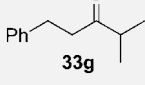
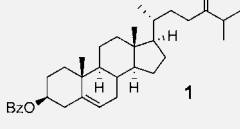




2.2. Asymmetric reduction of acyl silanes

α -Hydroxy silanes are useful building blocks in organic synthesis.¹⁷ Optically active hydroxy silanes have been employed as a chiral auxiliary for oxocarbenium ion,¹⁸ and they have been used for the synthesis of chiral alcohol by rearrangement of α -acetoxy silane.¹⁹ The present method for reduction of ketone with chiral alcohol **2** was applied to asymmetric reduction²⁰ of acyl silanes²¹ for synthesis of optically active α -hydroxy silanes.

Attempted reduction of acyl silane **35** by using diol **2** and DNBSA in the presence of octanethiol did not give the desired α -hydroxy silane **36** at all, and alkenyl sulfide **37** was obtained in 25% yield (Eq. 1). The formation of alkenyl sulfide by the reaction of acyl silane and thiol has already been reported,²² and this result suggested that the reaction of acyl silane **35** and octanethiol took place preferentially compared to the reduction of acyl silane **35** with diol **2**. Therefore, the reduction of **35** with diol **2** was carried out in the absence of octanethiol. It was surprisingly found that the reduction of **35** proceeded very smoothly to afford α -hydroxy silane **34** in 83% yield with high enantioselectivity (98% ee (*R*), Eq. 2). This result suggested that the reduction of acyl silane **35** with diol **2** proceeded more rapidly than the reaction with pent-3-en-2-one, which is formed from diol **2** (see Scheme 2). The high reactivity of acyl silane can be ascribed to its higher HOMO level, which is caused by interaction of the C–Si bond (σ_{C-Si}) with lone pair electrons of the carbonyl group (n_O).²³

Asymmetric reduction of various acyl silanes **38** was performed by using chiral diol **2** and a catalytic amount of DNBSA in benzene at reflux (Table 8). Asymmetric reduction of octanoyl silanes **38a–c** bearing a trimethylsilyl, *tert*-butyldimethylsilyl, or dimethylphenylsilyl group proceeded smoothly to afford the corresponding α -hydroxy silanes **39a–c** in good yields with high enantioselectivities (entries 1–3). It was noted that asymmetric reduction of acetyl silane **38d** proceeded within 5 min, and alcohol **38d** was obtained in 85% yield with 95% ee (entry 5), while prolonged reaction time (10 min) resulted in 77% yield of **39d** with 75% ee. Thus, the formed α -hydroxy silane **39d** was decomposed by extending the reaction time, and partial racemization took place. Reduction of β -branched acyl silane **38e** proceeded in 55% yield with 97% ee

Table 7
Asymmetric reduction of various ketones **33** using diol **2** and DNBSA^a

Entry	Ketone	Product	Yield ^b (%)	ee ^c (%)
1		34a	18 ^c	>99
2		6	21 ^d	>99
3		34b	36	99
4		34c	57	93
5		34d	52	87
6		34e	50	82
7		34f	42	82
8		34g	26 ^d	66
9		4	24 ^d	24- <i>R/S</i> =88:12
10		34h	50	51
11		34i	60	52
12		34j	64	51
13		34k	0	—

^a Ketone (1.0 equiv), diol **2** (1.1 equiv), C₈H₁₇SH (1.1 equiv), and DNBSA (5 mol %) were refluxed in benzene using a Dean–Stark apparatus.

^b Determined by ¹H NMR analysis using an internal standard.

^c Determined by chiral HPLC (see Experimental section).

^d Isolated yield.

(entry 5), but the reduction of α -branched acyl silane **38f** did not proceed (entry 6). Reduction of enoyl silane **38g** did not give the desired α -hydroxy silane **39g**, probably due to dehydration of **39g**

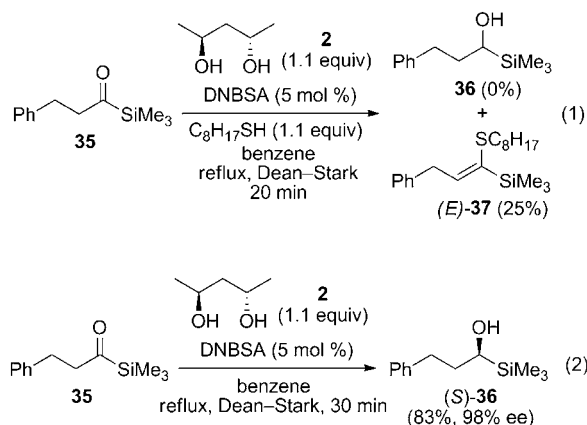


Table 8
Asymmetric reduction of various acyl silanes **38** using diol **2** and DNBSA^a

Entry	Acyl silanes 38	Time (min)	Product 39	Yield ^b (%)	ee ^c (%)
1		30		81	98
2		60		74	99
3		30		78	92
4		5		85	95
5		120		51	97
6		180		0	—
7		10		0	—
8		90		17	74

^a For conditions, see Eq. 2.

^b Isolated yield.

^c Determined by chiral HPLC (see Experimental section).

under acidic conditions (entry 7). Asymmetric reduction of benzoyl silane **38h** proceeded very slowly, and the desired product **39h** was obtained in only 17% yield with 74% ee (entry 8).

3. Conclusion

Asymmetric reduction of aliphatic ketones proceeded by reaction with chiral pentane-2,4-diol **2** in the presence of octanethiol and a catalytic amount of DNBSA in benzene at reflux. On the other hand, asymmetric reduction of various acyl silanes using DNBSA

and diol **2** proceeded efficiently in the absence of octanethiol. Highly asymmetric induction was observed when two substituents attached on the carbonyl group of ketone and acyl silane were sterically well-differentiated, and reduction of ketones and acyl silanes bearing less-hindered substituents proceeded more smoothly. It is generally believed that Brønsted acid-catalyzed reaction of ketone and 1,3-diol gives the corresponding acetal, but the present findings show that reduction can take place when a strong Brønsted acid and some *anti*-1,3-diols are employed.

4. Experimental section

4.1. General

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100. ¹H NMR spectra were recorded on a JEOL JNM EX270 (270 MHz), JEOL JNM ECS400 (400 MHz), JEOL JNM GSX500 (500 MHz), or JEOL JNM ECA600 (600 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. ¹³C NMR spectra were recorded on a JEOL JNM EX270 (67.5 MHz), JEOL JNM ECS400 (100 MHz), JEOL JNM GSX500 (125 MHz), or JEOL JNM ECA600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with solvent resonance as the internal standard CDCl₃. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102A mass spectrometer (EI). Elemental analyses were carried out on a Yanaco CHN Corder MT-5. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm). Silica gel column chromatography was carried out on silica gel 60 N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μ m). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. (2*S*,4*S*)-Pentane-2,4-diol (**2**) was purchased from Wako Pure Chemical Industries, Ltd. and used without purification (Lot No. ALQ4465, 97.0% ee, $[\alpha]_D^{20} +52.9$ (c 10, EtOH)). Characterization data of compounds **3**, **4**, **6**, **8**, **16**, **29d**, **30d**, **34c–f**, **36**, and **39a–d** were reported.⁴ Diols **15a**,²⁴ **15b**,²⁵ **15c**,²⁵ **15d**,²⁵ and **15e**²⁶ are known compounds. Acyl silanes **35**,²⁷ **38a**,²⁸ **38b**,²⁹ **38c**,³⁰ **38d**,³⁰ **38e**,³¹ **38f**,³¹ **38g**,³¹ and **38h**³² were prepared by the reported procedure.²⁷ The absolute configuration was determined by converting alcohol to the corresponding MTPA ester.³³

4.1.1. (4*R*,5*R*)-4,5-Dimethyl-2-methyl-2-(2-phenylethyl)-1,3-dioxolane (17). To a stirred mixture of **7** (50.2 mg, 0.34 mmol) and (2*R*,3*R*)-butanediol **12** (34.2 mg, 0.38 mmol) in dry benzene (10 mL) was added 2,4-dinitrobenzenesulfonic acid (4.9 mg, 0.017 mmol) and the mixture was refluxed for 0.5 h with continuous azeotropic removal of water. After cooling to room temperature, the reaction was quenched with saturated aqueous NaHCO₃ solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative TLC (hexane/ethyl acetate=5:1) to afford **17** (41.7 mg, 0.19 mmol, 56%) as a colorless oil; ¹H NMR (600 MHz, CDCl₃) δ 1.26 (d, $J=2.7$ Hz, 3H), 1.27 (d, $J=3.4$ Hz, 3H), 1.40 (s, 9H), 1.96 (m, 2H), 2.69–2.78 (m, 2H), 3.60–3.64 (m, 1H), 3.69–3.72 (m, 1H), 7.16–7.21 (m, 3H), 7.24–7.28 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 16.4, 17.2, 25.9, 30.1, 42.2, 78.1, 79.0, 108.7, 125.6, 128.3, 142.2; IR (CHCl₃, cm⁻¹) 1604, 1454; HRMS (EI⁺) calcd for C₁₄H₂₀O₂ (m/z) 220.14633, found 220.14580.

4.1.2. 2,8-Dimethylnon-5-en-4-one (19). Obtained as a colorless oil: ¹H NMR (600 MHz, CDCl₃) δ 0.92 (d, $J=4.8$ Hz, 6H), 0.94 (d, $J=4.8$ Hz,

6H), 1.77 (sep, $J=6.9$ Hz, 1H), 2.10 (t, $J=7.6$ Hz, 2H), 2.15 (m, 1H), 2.40 (d, $J=6.9$ Hz, 2H), 6.07 (d, $J=15.8$ Hz, 1H), 6.79 (dt, $J=15.8, 7.6$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 22.4, 22.7, 25.2, 27.9, 41.7, 49.1, 131.8, 146.2, 200.6; IR (CHCl_3 , cm^{-1}) 1662, 1623, 1465; HRMS (EI^+) calcd for $\text{C}_{11}\text{H}_{20}\text{O}$ (m/z) 168.15142, found 168.15127.

4.1.3. 4-Octylsulfanylpentan-2-one (29d). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.24–1.32 (m, 10H), 1.35–1.38 (m, 3H), 1.57 (quin, $J=7.56$, 2H), 2.16 (s, 3H), 2.52 (t, $J=7.56$, 2H), 2.57 (dd, $J=8.2, 17.2$ Hz, 1H), 2.73 (dd, $J=6.2, 17.2$ Hz, 1H), 3.23 (sex, $J=6.2$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 14.0, 21.5, 22.5, 28.8, 28.9, 29.0, 29.6, 30.5, 30.6, 31.7, 34.8, 50.9, 206.6; IR (CHCl_3 , cm^{-1}) 1713, 1456; HRMS (EI^+) calcd for $\text{C}_{13}\text{H}_{26}\text{SO}$ (m/z) 230.17044, found 230.17032.

4.1.4. 4-Octylsulfanylpentan-2-ol (30d). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3 , a mixture of diastereomers, 57:43) δ 0.88 (t, $J=6.9$ Hz, 3H), 1.20 (d, $J=6.2$ Hz, 3H), 1.25–1.40 (m, 13H), 1.55–1.61 (m, 3H), 1.65–1.71 (m, 1H), 2.55 (t, $J=7.6$ Hz, 2H), 2.87 (sex, $J=6.9$ Hz, 0.44H), 2.98 (sex, $J=6.9$ Hz, 0.59H), 3.96 (m, 0.44H), 4.11 (m, 0.58H); ^{13}C NMR (150 MHz, CDCl_3) δ 14.1, 22.1, 22.2, 23.7, 23.9, 29.0, 29.1, 29.2, 29.7, 29.8, 29.9, 30.2, 31.8, 37.0, 38.1, 45.2, 45.7, 65.4, 67.0; IR (CHCl_3 , cm^{-1}) 3567, 1456; HRMS (EI^+) calcd for $\text{C}_{13}\text{H}_{28}\text{SO}$ (m/z) 232.18609, found 232.18592.

4.1.5. 5-Octylsulfanylheptan-3-one (31a). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 0.88 (t, $J=7.6$ Hz, 3H), 0.98 (t, $J=7.6$ Hz, 3H), 1.07 (t, $J=7.6$ Hz, 3H), 1.24–1.38 (m, 10H), 1.53–1.62 (m, 4H), 2.41–2.50 (m, 4H), 2.59 (dd, $J=6.2, 16.5$ Hz, 1H), 2.67 (dd, $J=7.6, 16.5$ Hz, 1H), 3.07 (quin, $J=6.2$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 7.6, 11.2, 14.1, 22.6, 28.2, 29.0, 29.2, 29.8, 31.1, 31.8, 37.0, 42.4, 48.0, 209.8; IR (CHCl_3 , cm^{-1}) 1712, 1459; HRMS (EI^+) calcd for $\text{C}_{13}\text{H}_{26}\text{SO}$ (m/z) 230.17044, found 230.17032.

4.1.6. 2,6-Dimethyl-5-octylsulfanylheptan-3-one (31b). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 0.88 (t, $J=6.9$ Hz, 3H), 0.92 (d, $J=6.2$ Hz, 3H), 0.99 (d, $J=6.9$ Hz, 3H), 1.10 (d, $J=2.1$, 3H), 1.12 (d, $J=2.1$ Hz, 3H), 1.24–1.38 (m, 10H), 1.53 (quin, $J=7.6$ Hz, 2H), 1.88 (m, 1H), 2.50 (t, $J=7.6$ Hz, 1H), 2.60–2.65 (m, 2H), 2.71 (dd, $J=8.9, 17.2$ Hz, 1H), 3.07 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 14.1, 17.9, 18.0, 18.9, 19.6, 22.6, 28.9, 29.2, 29.8, 31.8, 32.4, 32.9, 41.6, 44.1, 47.8, 213.1; IR (CHCl_3 , cm^{-1}) 1713, 1456; HRMS (EI^+) calcd for $\text{C}_{17}\text{H}_{34}\text{SO}$ (m/z) 286.23304, found 286.23319.

4.1.7. 2,8-Dimethyl-6-octylsulfanylnonan-4-one (31d). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 0.86–0.92 (m, 15H), 1.24–1.42 (m, 12H), 1.53–1.57 (m, 2H), 1.81 (m, 1H), 2.15 (sep, $J=6.9$ Hz, 1H), 2.30 (dd, $J=2.7, 6.9$ Hz, 2H), 2.48 (td, $J=6.9, 4.8$ Hz, 2H), 2.55 (dd, $J=6.9, 17.2$ Hz, 1H), 2.68 (dd, $J=6.9, 17.2$ Hz, 1H), 3.14 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 14.1, 22.0, 22.6, 22.7, 22.9, 24.4, 25.5, 29.0, 29.2, 29.7, 30.6, 31.8, 38.5, 44.8, 50.0, 52.7, 209.1; IR (CHCl_3 , cm^{-1}) 1708, 1467; HRMS (EI^+) calcd for $\text{C}_{19}\text{H}_{38}\text{SO}$ (m/z) 314.26434, found 314.26412.

4.1.8. 6-Octylsulfanylnonan-4-one (31f). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 0.88 (t, $J=6.9$ Hz, 3H), 0.89–0.93 (m, 6H), 1.24–1.32 (m, 8H), 1.34–1.64 (m, 10H), 2.40 (td, $J=6.9, 4.8$ Hz, 2H), 2.49 (td, $J=7.6, 2.1$ Hz, 2H), 2.60 (dd, $J=6.9, 17.2$ Hz, 1H), 2.67 (dd, $J=6.9, 17.2$ Hz, 1H), 3.11 (quin, $J=6.9$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 13.7, 13.9, 14.1, 17.1, 20.0, 22.6, 29.0, 29.2, 29.8, 31.0, 31.8, 37.6, 40.4, 45.7, 48.9, 209.4; IR (CHCl_3 , cm^{-1}) 1710, 1465; HRMS (EI^+) calcd for $\text{C}_{17}\text{H}_{34}\text{SO}$ (m/z) 286.23304, found 286.23317.

4.1.9. 5-Octylsulfanylheptan-3-ol (32a). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3 , a mixture of diastereomers, 56:44) δ 0.88 (t, $J=6.9$ Hz, 3H), 0.94–0.97 (m, 3H), 0.98–1.02 (m, 3H), 1.22–1.72

(m, 18H), 2.15 (br s, 0.33H), 2.48–2.55 (m, 2H), 2.62–2.67 (m, 0.55H), 2.78 (dtd, $J=4.1, 6.9, 9.6$ Hz, 0.43H), 2.92 (br s, 0.46H), 3.70 (m, 0.54H), 3.87 (m, 0.42H); ^{13}C NMR (150 MHz, CDCl_3) δ 9.8, 10.0, 11.0, 11.4, 14.1, 22.6; IR (CHCl_3 , cm^{-1}) 3417, 1463; HRMS (EI^+) calcd for $\text{C}_{15}\text{H}_{32}\text{SO}$ (m/z) 260.21739, found 260.21735.

4.1.10. 6-Octylsulfanylnonan-4-ol (32f). Obtained as a colorless oil: ^1H NMR (600 MHz, CDCl_3 , a mixture of diastereomers, 55:45) δ 0.88 (t, $J=6.9$ Hz, 3H), 0.91–0.94 (m, 6H), 1.22–1.32 (m, 9H), 1.34–1.72 (m, 13H), 2.21 (br s, 0.37H), 2.46–2.55 (m, 2H), 2.68 (m, 0.54H), 2.84 (m, 0.45H), 2.95 (br s, 0.46H), 3.78 (m, 0.53H), 3.95 (m, 0.43H); ^{13}C NMR (150 MHz, CDCl_3) δ 14.00, 14.09, 18.66, 19.82, 20.11, 22.64, 29.04, 29.06, 29.16, 29.18, 29.20, 29.76, 29.78, 29.83, 30.10, 31.80, 37.97, 38.00, 40.04, 40.06, 41.24, 42.05, 42.29, 44.28, 69.04, 71.30; IR (CHCl_3 , cm^{-1}) 3419, 1465; HRMS (EI^+) calcd for $\text{C}_{17}\text{H}_{36}\text{SO}$ (m/z) 288.24869, found 288.24866.

4.2. General procedure for asymmetric reduction of ketones (Table 7, entry 4)

To a stirred mixture of **33c** (49.4 mg, 0.44 mmol), (2S,4S)-pentane-2,4-diol (**2**) (49.8 mg, 0.48 mmol), and 2,4-dinitrobenzenesulfonic acid (DNBSA, 6.3 mg, 0.022 mmol) in dry benzene (5 mL) was added a solution of 1-octanethiol (70.5 mg, 0.48 mmol) in dry benzene (5 mL), and the mixture was refluxed for 1.5 h with continuous azeotropic removal of water. After cooling to room temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}=40/1$) to afford **34c** (28.5 mg, 0.25 mmol 57%) as a colorless oil.

4.2.1. (R)-3,3-Dimethyl-4-phenyl-butan-2-ol (34a)³⁴. Compound **34a** (>99% ee (R)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column. Chiral HPLC: Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/ i -PrOH) 40:1, flow rate: 0.5 mL/min, retention time (min) 14.4 (R isomer). $[\alpha]_{\text{D}}^{22} -7.93$ (c 1.9, CHCl_3) (lit.³⁴ $[\alpha]_{\text{D}} -4.66$ (c 3.0, CHCl_3)); ^1H NMR (600 MHz, CDCl_3) δ 0.80 (s, 3H), 0.86 (s, 3H), 1.16 (d, $J=6.2$ Hz, 3H), 2.50 (d, $J=13.1$ Hz, 1H), 2.68 (d, $J=13.1$ Hz, 1H), 3.53 (q, $J=6.2$ Hz, 1H), 7.16–7.21 (m, 3H), 7.25–7.28 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ : 17.9, 21.7, 23.0, 38.6, 44.5, 73.7, 125.8, 127.7, 130.5, 138.9.

4.2.2. (R)-2,2-Dimethylcyclopentanol (34b)³⁵. Compound **34b** (99% ee (R)) was obtained as a colorless oil. The enantiomeric excess (93% ee) was determined by HPLC analysis using a chiral column after derivatization to the corresponding p -nitrobenzoate. Chiral HPLC: Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/ i -PrOH) 200:1, flow rate: 0.5 mL/min, retention time (min) 13.3 (S isomer), 14.4 (R isomer). $[\alpha]_{\text{D}}^{23} -19.49$ (c 0.9, benzene) (lit.³⁵ $[\alpha]_{\text{D}} -15.8$ (c 10.1, benzene)); ^1H NMR (600 MHz, CDCl_3) δ 0.94 (s, 3H), 0.96 (s, 3H), 1.35–1.40 (m, 1H), 1.52–1.62 (m, 1H), 1.68–1.77 (m, 1H), 2.00–2.05 (m, 1H), 3.67 (t, $J=5.5$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 19.8, 21.2, 26.6, 32.6, 37.4, 42.0, 81.2.

4.2.3. (R)-2-Methyl-5-phenyl-3-pentanol (34g)³⁶. Compound **34g** (66% ee (R)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/ i -PrOH) 20:1, flow rate: 0.5 mL/min, retention time (min) 10.2 (S isomer), 10.9 (R isomer). $[\alpha]_{\text{D}}^{30} +25.19$ (c 3.0, EtOH); ^1H NMR (500 MHz, CDCl_3) δ 0.90 (d, $J=6.8$ Hz, 6H), 1.61

(br s, 1H), 1.67 (m, 1H), 2.63 (m, 1H), 2.83 (ddd, $J=5.2, 10.0, 13.7$ Hz, 1H), 3.37 (ddd, $J=3.6, 5.2, 8.8$ Hz, 1H), 7.15–7.21 (m, 3H), 7.25–7.28 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 17.1, 18.7, 32.4, 33.6, 35.9, 76.0, 125.7, 128.3, 128.4, 142.3.

4.2.4. (R)-Heptan-2-ol (34h)³⁷. Compound **34h** (51% ee (*R*)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiral HPLC: Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/*i*-PrOH) 200:1, flow rate: 0.5 mL/min, retention time (min) 6.6 (*R* isomer), 7.3 (*S* isomer). $[\alpha]_{\text{D}}^{20} -5.54$ (c 0.67, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 0.89 (t, $J=6.9$ Hz, 3H), 1.17 (d, $J=6.0$ Hz, 3H), 1.26–1.48 (m, 9H), 3.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.6, 23.3, 25.4, 31.8, 39.2, 68.0.

4.2.5. (R)-Octan-2-ol (34i)³⁵. Compound **34i** (52% ee (*R*)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiral HPLC: Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/*i*-PrOH) 300:1, flow rate: 0.5 mL/min, retention time (min): 6.6 (*R* isomer), 7.2 (*S* isomer). $[\alpha]_{\text{D}}^{20} -4.19$ (c 1.0, CHCl_3) (lit.³⁵ $[\alpha]_{\text{D}} -5.8$ (c 8.8, CHCl_3)); ^1H NMR (400 MHz, CDCl_3) δ 0.89 (m, 3H), 1.17 (d, $J=5.5$ Hz, 3H), 1.22–1.50 (m, 10H), 1.95 (br s, 1H), 3.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.5, 23.3, 25.7, 29.3, 31.8, 39.3, 68.0.

4.2.6. (R)-Nonane-2-ol (34j)³⁸. Compound **34j** (51% ee (*R*)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiral HPLC: Daicel Chiralpak AD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/*i*-PrOH) 300:1, flow rate: 0.5 mL/min, retention time (min): 6.40 (*R* isomer), 6.87 (*S* isomer). $[\alpha]_{\text{D}}^{23} -6.35$ (c 0.88, CHCl_3) (lit.³⁸ $[\alpha]_{\text{D}} -6.95$ (c 1.1, CHCl_3)); ^1H NMR (600 MHz, CDCl_3) δ 0.88 (t, $J=6.5$ Hz, 3H), 1.18 (d, $J=6.2$ Hz, 3H), 1.25–1.58 (m, 13H), 3.79 (sex, $J=1$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 14.1, 22.6, 23.4, 25.7, 29.3, 29.6, 31.8, 39.3, 68.2.

4.2.7. (Z)-1-Octylsulfanyl-3-phenyl-1-trimethylsilylprop-1-en (37). To a stirred mixture of **35** (49.4 mg, 0.24 mmol), (2*S*,4*S*)-pentane-2,4-diol **2** (28.5 mg, 0.27 mmol) and 2,4-dinitrobenzenesulfonic acid (DNBSA, 3.4 mg, 0.012 mmol) in dry benzene (5 mL) was added a solution of 1-octanethiol (70.5 mg, 0.48 mmol) in dry benzene (5 mL), and the mixture was refluxed for 20 min with continuous azeotropic removal of water. After cooling to room temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative TLC (hexane/benzene=20:1) to afford **37** (20.2 mg, 0.060 mmol, 25%) as a colorless oil; ^1H NMR (600 MHz, CDCl_3) δ 0.17 (s, 9H), 0.88 (t, $J=6.9$ Hz, 3H), 1.22–1.40 (m, 10H), 1.57 (quin, $J=7.6$ Hz, 2H), 2.65 (t, $J=7.6$ Hz, 2H), 3.78 (d, $J=6.2$ Hz, 2H), 6.37 (t, $J=6.9$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ -0.7, 14.1, 22.6, 28.8, 29.1, 29.2, 30.1, 31.8, 34.6, 36.9, 125.9, 128.4, 136.9, 140.3, 146.2; IR (CHCl_3 , cm^{-1}) 1602, 1247; HRMS (EI^+) calcd for $\text{C}_{13}\text{H}_{26}\text{SO}$ (m/z) 230.17044, found 230.17032. The (*Z*)-configuration was determined by NOE experiments (between $\text{CH}=\text{C}$ and Me_3Si).

4.3. General procedure for asymmetric reduction of acyl silanes (Eq. 2)

To a stirred mixture of **35** (77.0 mg, 0.37 mmol) and (2*S*,4*S*)-pentane-2,4-diol **2** (42.2 mg, 0.40 mmol) in dry benzene (10 mL) was added 2,4-dinitrobenzenesulfonic acid (DNBSA, 5.3 mg, 0.019 mmol),

and the mixture was heated at reflux for 0.5 h with continuous azeotropic removal of water. After cooling to room temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=20/1) to afford **36**⁴ (64.3 mg, 0.31 mmol 83%) as a colorless oil.

4.3.1. (S)-1-tert-Butyldimethylsilyl-3-methylbutan-1-ol (39e). Compound **39e** (97% ee (*S*)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding *p*-nitrobenzoate. Chiral HPLC: Daicel Chiralpak OD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/*i*-PrOH) 400:1, flow rate: 0.5 mL/min, retention time (min): 7.4 (*R* isomer), 10.7 (*S* isomer). $[\alpha]_{\text{D}}^{20} +19.46$ (c 0.8, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ -0.06 (s, 3H), 0.01 (s, 3H), 0.90 (d, $J=6.9$ Hz, 3H), 0.94 (m, 12H), 1.17 (ddd, $J=2.3, 10.5, 14.2$ Hz, 1H), 1.58 (ddd, $J=2.3, 12.4, 14.2$ Hz, 1H), 1.80–1.90 (m, 1H), 3.59 (dd, $J=2.3, 12.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -8.7, -7.7, 16.8, 20.8, 24.0, 24.1, 27.1, 43.4, 61.9; IR (CHCl_3 , cm^{-1}) 1250, 1466, 3603.

4.3.2. (S)- α -(Trimethylsilyl) benzyl alcohol (39h)²⁴. Compound **39h** (74% ee (*S*)) was obtained as a colorless oil. The enantiomeric excess was determined by HPLC analysis using a chiral column Daicel Chiralpak OD-H 46×150 mm, 254 nm UV detector, room temperature, eluent: (hexane/*i*-PrOH) 20:1, flow rate: 0.5 mL/min, retention time (min): 8.85 (*S* isomer), 12.2 (*R* isomer). $[\alpha]_{\text{D}}^{30} -59.37$ (c 0.16, CHCl_3) (lit.^{20c} $[\alpha]_{\text{D}} -79.7$ (c 1.08, CHCl_3)); ^1H NMR (600 MHz, CDCl_3) δ 0.02 (s, 9H), 1.68 (br s, 1H), 4.53 (s, 1H), 7.16–7.20 (m, 3H), 7.30–7.32 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ -4.2, 70.6, 124.9, 125.8, 128.1, 144.2.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors thank Teijin Pharma Ltd. for financial support and also thank Dr. Osamu Nishikawa, Mr. Kenzo Watanabe, Mr. Jun-ichi Oshida, and Mr. Toru Minoshima (all in Teijin Pharma Ltd.) for discussions.

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