Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10439–10444

TETRAHEDRON

Lewis acid-catalyzed asymmetric hydroxymethylation of silicon enolates in aqueous media

Kei Manabe, Shunpei Ishikawa, Tomoaki Hamada and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 28 April 2003; accepted 30 June 2003

Abstract—Asymmetric hydroxymethylation of silicon enolates with formaldehyde in aqueous media has been achieved using praseodymium triflate and a chiral crown ether. Formaldehyde aqueous solution can be directly used for the reactions, and a water/THF mixture was found to be the best solvent system. This is the first example of catalytic asymmetric hydroxymethylation of silicon enolates.

1. Introduction

Asymmetric aldol reaction is one of the most useful carbon–carbon bond-forming reactions to afford optically active β-hydroxy carbonyl compounds.[1] In recent years, several enantioselective aldol reactions have been developed to pursue efficiency in obtaining these chiral compounds. Among them, chiral Lewis acid-mediated asymmetric aldol reactions of aldehydes with silicon enolates (asymmetric Mukaiyama aldol reactions)[2] have been elaborated into a most convenient asymmetric aldol methodology starting from achiral substrates to create asymmetric centers at the β-positions or the α- and β-positions of the aldol adducts. On the other hand, formaldehyde is one of the most important C1 electrophiles in organic synthesis.[3] If formaldehyde can be used in the asymmetric Mukaiyama aldol reactions, a direct and efficient method to introduce a C1 functional group with constructing an asymmetric center only at the α-position of the carbonyl group would be provided. However, catalytic asymmetric Mukaiyama-type hydroxymethylation has been unprecedented as far as we know. As for catalytic asymmetric hydroxymethylation, a couple of examples without using silicon enolates have been reported. Fujii et al. reported the reactions of 2-nitrocyclohexanone using cinchona alkaloids as catalysts,[4] and Ito et al. reported the reactions of 2-cyanopropionates catalyzed by a rhodium(I) complex coordinated with *trans*-chelating chiral diphosphine TRAP.[5] However, both groups used substrates which were limited to those having active-methine groups to create asymmetric quaternary centers. It is difficult to synthesize hydroxymethylated compounds with asymmetric tertiary centers by their methods. To achieve substrate generality, therefore, development of Lewis acid-catalyzed, Mukaiyama-type hydroxymethylation is desired.

In conventional methods of the Mukaiyama-type hydroxymethylation in organic solvents, gaseous formaldehyde is often generated before use from paraformaldehyde with tedious procedures.[6] In addition, formaldehyde gas known as the causative material of the 'sick house syndrome' is harmful to health. On the other hand, commercial formaldehyde aqueous solution is cheap, easy to handle, and stable. However, large amounts of water in the aqueous solution have inhibited the hydroxymethylation because of the instability of conventional Lewis acids such as $TiCl_4$. Therefore, if the catalysts work well in the presence of water, aqueous media are attractive as the solvents of the hydroxymethylation.[7] In recent years, indeed, organic reactions in aqueous media have become a very important field of study because of the easy procedures and unique reactivity and selectivity.[8] Along these lines, catalytic hydroxymethylation using $Yb(OTf)_3$ in aqueous THF was first demonstrated by us.[9] We have also developed various types of lanthanide triflates ($Ln(OTf)_3$)-catalyzed reactions in aqueous media.[10] $Ln(OTf)_3$ can be easily recovered after the reactions are completed, and reused. Recently, we have also achieved catalytic asymmetric aldol reactions using $Ln(OTf)_3$ as the Lewis acid catalyst and chiral crown ether **1** as a ligand in aqueous media.[11] In these reactions, the aldol adducts were obtained in high yields with high diastereo- and enantioselectivities. We envisioned that the catalytic system of $Ln(OTf)_3$ and **1** would be also effective for asymmetric hydroxymethylation. In this paper, we report the first example of Lewis acid-catalyzed asymmetric hydroxymethylation of silicon enolates using formaldehyde aqueous solution in the presence of **1** as the ligand (Fig. 1).

Keywords: Lewis acid; aldol reaction; hydroxymethylation.
* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

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doi:10.1016/j.tet.2003.06.007

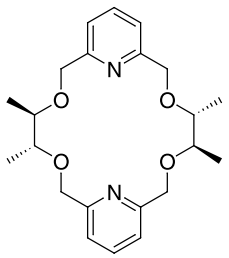

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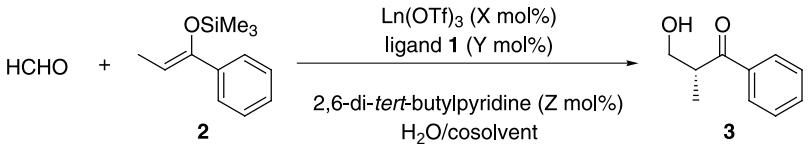
Figure 1. Chiral crown ether.

2. Results and discussion

Catalytic asymmetric aldol reactions of silicon enolates have been difficult to achieve in aqueous media. The main problem is that competitive ligand exchange between a chiral ligand and water easily occurs, and that this promotes achiral free Lewis acid-catalyzed pathways. On the other hand, in the catalytic asymmetric aldol reactions in aqueous media using the combination of **1** and $Ln(OTf)_3$, **1** was proved to be the clue towards overcoming this problem because **1** coordinated to the Ln cations strongly enough and did not significantly reduce their Lewis acidity. Therefore, we decided to apply this catalytic system to asymmetric hydroxymethylation of silicon enolates.

First, we examined the reaction of formaldehyde (commercially available 35%, w/w aqueous solution) with silyl enol ether **2** derived from propiophenone using 10 mol% of $Pr(OTf)_3$ and 12 mol% of **1** in H_2O/EtOH at 0°C (Table 1, entry 1). However, only a trace amount of the product was obtained. In this reaction, rapid hydrolysis of the silyl enol ether was observed. In our previous work on the catalytic asymmetric aldol reactions of ketene silyl acetals which were relatively unstable in aqueous media, 2,6-di-*tert*-butylpyridine was found to be effective for preventing the hydrolysis of the ketene silyl acetals without decreasing the selectivity.[11b] When 2,6-di-*tert*-butylpyridine was used in the present system, the yield was increased to 14% (entry 2). To improve the yield further, we changed the solvent system to H_2O/THF, and as a result, the yield increased while the selectivity was not affected (entry 3). We next examined the amount of formaldehyde (entries 3–6). Interestingly, the amount of formaldehyde affected the selectivity, and the best selectivity was obtained when 10 equiv. of formaldehyde were used. Next, we investigated the amounts of the catalyst and reaction temperature (entries 7 and 8). When the amounts of the catalyst were increased, the selectivity was slightly improved. Furthermore, the yield was dramatically improved up to 87% at 30°C with slight increase in the selectivity compared with that at 0°C. We also tested other metal triflates (entry 9–11) whose ionic diameters (La: 2.43 Å, Ce: 2.39 Å, Nd: 2.33 Å) were larger or smaller than that of Pr (2.36 Å), and the best result was obtained when $Pr(OTf)_3$ was employed. We also investigated other solvent systems (entry 12–16). In the case of $H_2O/{}^nBu_2O$, the system separated into two phases and the reaction proceeded sluggishly. This result indicated the possibility that formaldehyde existed in the aqueous phase and did not encounter the silyl enol ether which was in the organic phase. Therefore, homogeneous solutions such as H_2O/THF and H_2O/DME were tested, and it was found that the reactions proceeded smoothly in these solvents. The best ee was obtained in H_2O/EtOH, although marked decrease in the yield occurred because of the rapid hydrolysis of the silyl enol ether even in the presence of 2,6-di-*tert*-butylpyridine (entry 16). It should be noted that 2,6-di-*tert*-butylpyridine was not essential in an aqueous THF solution as shown in entry 17. Although the selectivity in this catalytic system still remains moderate, this is the first example of catalytic asymmetric Mukaiyama-type hydroxymethylation. Moreover, it is exciting to obtain such a result

Table 1. Investigations of reaction conditions



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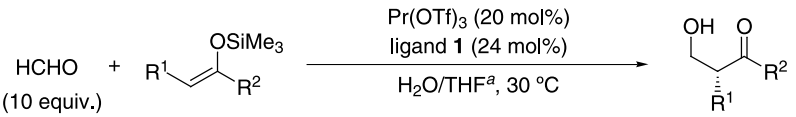
Entry	HCHO (equiv.)	Ln (*X*)	*Y*	*Z*	Cosolvent[a]	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	5	Pr (10)	12	0	EtOH	0	63	Trace	24
2	5	Pr (10)	12	30	EtOH	0	34	14	29
3	5	Pr (10)	12	30	THF	0	18	26	29
4	2.5	Pr (10)	12	30	THF	0	18	17	22
5	10	Pr (10)	12	30	THF	0	18	31	39
6	30[b]	Pr (10)	12	30	THF	0	18	56	30
7	10	Pr (20)	24	100	THF	0	18	34	43
8	10	Pr (20)	24	100	THF	30	18	87	48
9	10	La (20)	24	100	THF	30	18	73	39
10	10	Ce (20)	24	100	THF	30	18	83	47
11	10	Nd (20)	24	100	THF	30	18	81	44
12	10	Pr (20)	24	100	DME	30	18	79	47
13	10	Pr (20)	24	100	1,4-Dioxane	30	18	65	42
14	10	Pr (20)	24	100	$^nBu_2O$	30	18	Trace	–
15	10	Pr (20)	24	100	CH_3CN	30	22	61	36
16	10	Pr (20)	24	100	EtOH	30	18	57	55
17	10	Pr (20)	24	0	THF	30	18	91	48

[a] 172 mg of formalin aquous solution (35%, w/w) and 1.00 mL of cosolvent/0.200 mmol of the sily enol ether.
[b] 515 mg of formalin aquous solution (35%, w/w) and 1.00 mL of cosolvent/0.200 mmol of the sily enol ether.

Table 2. Investigation of substrate generality



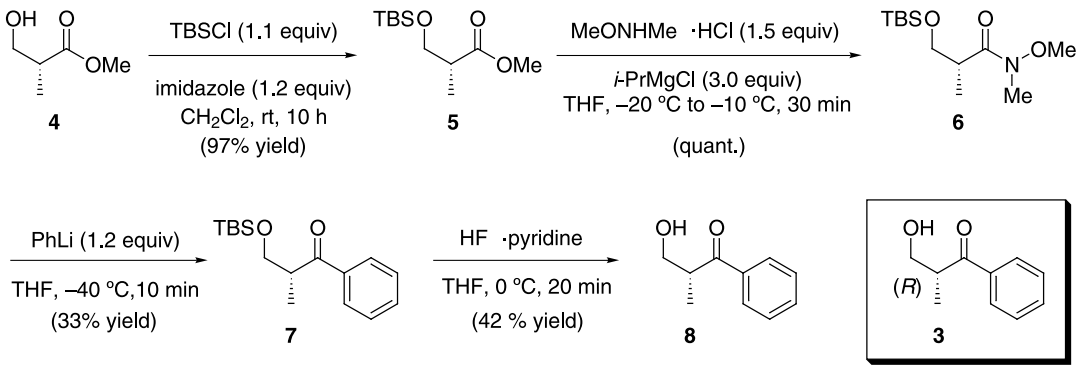
Entry	R^1	R^2	Time (h)	Yield (%)	ee (%)
1	Me	4-MeO–C_6H_4	18	78	41
2	Me	4-Cl–C_6H_4	33	86	44
3	Me	2,4,6-Me_3–C_6H_2	65	48	14
4	Me	3,5-Me_2–C_6H_3	22	92	43
5	Me	S^{t}Bu	18	52	54
6	Et	S^{t}Bu	65	68	45
7	Me	S^{i}Pr	18	40	23

[a]1.00 mL of cosolvent/0.200 mmol of the silyl enol ether.

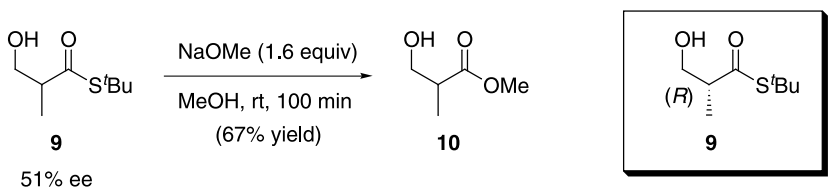
because it has been known to be difficult to construct asymmetric centers only at the α-position of the aldol adducts using chiral Lewis acid catalysts.

We next performed catalytic asymmetric hydroxymethylation using several substrates under the optimized conditions mentioned above (Table 1, entry 17), and the results are summarized in Table 2. In the case of *para*-substituted propiophenone (entries 1 and 2), both electron-donating and electron-withdrawing substituents slightly decreased the selectivity compared with that of the unsubstituted propiophenone. Furthermore, in the case of an electron-withdrawing chloro group, a slight decrease in the reaction rate was observed probably because of the electronic effect. In the case of the silicon enolate derived from ethyl mesityl ketone (entry 3), the reaction rate and the selectivity were both decreased. For the silicon enolate derived from 3,5-dimethyl propiophenone, high yield and modest selectivity were obtained. The ketene silyl acetal derived from *S*-*tert*-butyl propanethioate (entry 5) gave comparatively good selectivity (54% ee), while a slight decrease in the yield was observed. The ketene silyl acetal is less stable than the silyl enol ethers in aqueous solution, and hydrolysis of the ketene silyl acetal decreased the yield. In addition, it was revealed that the ethyl group at the α-position of the ketene silyl acetal decreased the reactivity and selectivity (entry 6). We changed the substituent on the sulfur of the ketene silyl acetal from *tert*-butyl to a less bulky isopropyl group expecting an increase in the reactivity (entry 7), but lower yield and selectivity were obtained.

The absolute configurations of the products were determined according to the following procedure. The product of the hydroxymethylation of **2** was determined to be (*R*)-form, comparing the retention time of HPLC with that of the optically pure material **8** which was prepared from commercially available (*R*)-(−)-3-hydroxyisobutyric acid methyl ester **4** as shown in Scheme 1. The hydroxy group of **4** was protected as its *tert*-butyldimethylsilyl ether **5**, which was converted to the Weinreb amide **6** according to the known procedure.[12] Phenyl ketone **7** was obtained by treatment of **6** with phenyllithium. Deprotection of the silyl group by HF· pyridine gave the desired product **8**. In all steps, no racemization was observed. The stereochemistry of the products of the other ketones in Table 2 was assumed to be the same by anology. On the other hand, product **9** (Scheme 2) was converted to the corresponding methyl ester by treatment with sodium methoxide. This transformation



Scheme 1. Determination of the absolute configuration of **3**.



Scheme 2. Determination of the absolute configuration of **9**.

was known in the previous investigation to give no epimerization.[11b] Comparison of the optical rotation of **10** (51% ee, $[\alpha]_D^{16.9}=-11.1$ (*c* 0.405, MeOH)) with that of **4** ($[\alpha]_D^{24}=-24.2$ (*c* 0.405, MeOH)) revealed that the product **9** had (*R*)-configuration. The stereochemistry of the products of the other thioesters in Table 2 was assumed to be the same by anology.

3. Conclusion

We have achieved chiral Lewis acid-catalyzed asymmetric hydroxymethylation of silicon enolates for the first time. In this reaction, the combination of $Pr(OTf)_3$ and **1** in aqueous THF at 30°C was found to be effective. This reaction provides an efficient way to an optically active α-hydroxymethyl carbonyl compound and its derivatives. It is noted that formaldehyde aqueous solution can be used successfully in this reaction. Although the enantioselectivities of the products remain to be improved, we believe that these results and the concepts of the methodologies will open the way for further progress in this field.

4. Experimental

4.1. General

Melting points were uncorrected. IR spectra were measured with JASCO FT/IR-610 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as an internal standard (δ=0) for ^1H NMR and $CDCl_3$ as an internal standard (δ=77.0) for ^{13}C NMR. Mass spectra were measured with SHIMADZU GCMS-QP5050A. Optical rotations were measured with a JASCO P-1010 polarimeter. The enantiomeric excess (ee) was determined by HPLC analysis using a chiral column. HPLC analysis was performed on following apparatuses; SHIMADZU LC-10AT (pump), and SHIMADZU SPD-10A (UV detector, measured at 254 nm), and SHIMADZU C-R6A or C-R8A (chromatopac). Preparative thin-layer chromatography was carried out using Wakogel B-5F.

4.2. General procedure of the asymmetric hydroxymethylation

To a solution of $Pr(OTf)_3$ (20 mol%) in THF 0.09 mL was added a solution of **1** (24 mol%) in THF (0.36 mL). Then, a formaldehyde aqueous solution (35%, w/w, 172 mg, 2.0 mmol) in THF (0.30 mL) and a solution of a silicon enolate (0.20 mmol) in THF (0.30 mL) were added at 30°C. The whole was stirred until the silicon enolate disappeared completely. The reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution. The mixture was extracted with methylene chloride three times, dried over Na_2SO_4, and concentrated. The desired product was purified by silica gel chromatography (AcOEt/hexane 1/4). The enantioselectivity of the hydroxymethylated adduct were determined by HPLC analysis.

4.2.1. 3-Hydroxy-1-(4-methoxyphenyl)-2-methylpropan-1-one. ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, *J*=7.1 Hz), 2.60 (brs), 3.62 (ddq, 1H, *J*=4.3, 7.0, 7.1 Hz), 3.78 (dd, 1H, *J*=4.3, 11.1 Hz), 3.87 (s, 3H), 3.91 (dd, 1H, *J*=7.0, 11.1 Hz), 6.95 (d, 2H, *J*=8.9 Hz), 7.95 (d, 2H, *J*=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 42.4, 55.4, 64.6, 113.8, 129.0, 130.7, 163.6, 202.9; IR (neat) 3438, 2933, 1667, 1597, 1251, 1173, 1047, 975, 843 cm^{-1}; MS *m/z* 194 (M^+). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.33; $[\alpha]_D^{24}=-13.7$ (*c* 1.23, EtOH) (41% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=19/1, flow rate=1.0 mL/min) assumed *R* isomer: t_R=39.8 min (major), assumed *S* isomer: t_R=31.1 min (minor).

4.2.2. 1-(4-Chlorophenyl)-3-hydroxy-2-methylpropan-1-one. ^1H NMR ($CDCl_3$) δ 1.21 (d, 3H, *J*=7.3 Hz), 2.52 (brs), 3.62 (ddq, 1H, *J*=4.3, 7.2, 7.3 Hz), 3.77 (dd, 1H, *J*=4.3, 11.1 Hz), 3.87 (s, 3H), 3.93 (dd, 1H, *J*=7.2, 11.1 Hz), 7.44 (d, 2H, *J*=8.5 Hz), 7.90 (d, 2H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 43.0, 64.4, 129.0, 129.8, 134.4, 139.7, 203.0; IR (neat) 3424, 2937, 1682, 1590, 1401, 1092, 976, 841 cm^{-1}; MS *m/z* 198 (M^+). Anal. calcd for $C_{10}H_{11}ClO_2$: C, 60.48; H, 5.58. Found: C, 60.18; H, 5.85; $[\alpha]_D^{24}=-15.7$ (*c* 1.65, EtOH) (44% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=19/1, flow rate=1.0 mL/min) assumed *R* isomer: t_R=27.2 min (major), assumed *S* isomer: t_R=18.2 min (minor).

4.2.3. 3-Hydroxy-2-methyl-1-(2,4,6-trimethylphenyl)-propan-1-one. ^1H NMR ($CDCl_3$) δ 1.14 (d, 3H, *J*=7.6 Hz), 2.22 (s, 6H), 2.28 (s, 3H), 3.13 (ddq, 1H, *J*=4.1, 6.8, 7.6 Hz), 3.80 (dd, 1H, *J*=4.1, 11.2 Hz), 3.90 (dd, 1H, *J*=6.8, 11.2 Hz), 6.85 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 12.9, 19.6, 21.0, 49.5, 64.0, 128.7, 133.3, 138.0, 138.7, 214.3; IR (neat) 3439, 2928, 1685, 1610, 1457, 1035, 973 cm^{-1}; MS *m/z* 206 (M^+). Anal. calcd for $C_{13}H_{19}O_2$: C, 75.69; H, 8.80. Found: C, 75.44; H, 8.80; $[\alpha]_D^{29}=-0.70$ (*c* 1.04, EtOH) (14% ee); HPLC (Daicel Chiralcell AS, hexane/*i*-PrOH=60/1, flow rate=0.5 mL/min) assumed *R* isomer: t_R=42.8 min (major), assumed *S* isomer: t_R=54.0 min (minor).

4.2.4. 3-Hydroxy-2-methyl-1-(3,5-dimethylphenyl)propan-1-one. ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, *J*=7.3 Hz), 2.31 (brs, 1H), 2.37 (s, 6H), 3.65 (ddq, 1H, *J*=4.1, 7.0, 7.3 Hz), 3.79 (dd, 1H, *J*=4.1, 11.0 Hz), 3.91 (dd, 1H, *J*=7.0, 11.0 Hz), 7.21 (s, 1H), 7.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.2, 42.9, 64.6, 126.1, 134.9, 136.3, 138.3, 204.9; IR (neat) 3433, 2931, 1678, 1027 cm^{-1}; MS *m/z* 192 (M^+). Anal. calcd for $C_{12}H_{16}O_2$: C, 75.97; H, 8.37. Found: C, 74.67; H, 8.57; $[\alpha]_D^{25}=-15.3$ (*c* 1.84, EtOH) (43% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=40/1, flow rate=1.0 mL/min) assumed *R* isomer: t_R=23.7 min (major), assumed *S* isomer: t_R=21.4 min (minor).

4.2.5. 3-Hydroxy-2-methyl-thiopropionic acid *S*-*tert*-butyl ester. ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, *J*=7.2 Hz), 1.47 (s, 9H), 2.06 (brs), 2.77 (ddq, 1H, *J*=4.6, 7.1, 7.2 Hz), 3.67 (dd, 1H, *J*=4.6, 11.2 Hz), 3.75 (dd, 1H, *J*=7.1, 11.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 29.8, 48.1, 50.7, 64.8, 204.2; IR (neat) 3403, 2967, 1682, 1456, 1364, 964 cm^{-1}; MS *m/z* 176 (M^+). Anal. calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15. Found: C, 54.45; H, 8.92; $[\alpha]_D^{26}=-24.4$ (*c* 0.71, EtOH) (54% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=100/1, flow rate=1.0 mL/min) *R* isomer: t_R=30.6 min (major), *S* isomer: t_R=40.3 min (minor).

4.2.6. 2-Hydroxymethyl-thiobutyric acid *S*-*tert*-butyl ester. ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.2 Hz), 1.48 (s, 9H), 1.52–1.78 (m, 2H), 2.00 (brs), 2.55–2.65 (m, 1H), 3.71 (dd, 1H, J=4.1, 11.1 Hz), 3.78 (dd, 1H, J=7.0, 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 11.6, 22.4, 29.8, 48.3, 57.8, 63.3. 203.9; IR (neat) 3407, 2966, 1681, 1456, 1364, 945 cm^{-1}; MS m/z 190 (M^+). Anal. calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; N, 0.00. Found: C, 57.05; H, 9.32; N, 0.00; $[\alpha]_D^{27}$=−2.5 (45% ee, c 1.25, EtOH); HPLC (Daicel Chiralpak ADH, hexane/*i*-PrOH=100/1, flow rate=1.0 mL/min) assumed *R* isomer: t_R=27.5 min (major), assumed *S* isomer: t_R=40.0 min (minor).

4.2.7. 3-Hydroxy-2-methyl-thiopropionic acid *S*-isopropyl ester. ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, J=7.1 Hz), 1.31 (d, 3H, J=6.8 Hz), 1.32 (d, 3H, J=7.1 Hz), 2.19 (brs), 2.82 (ddq, 1H, J=4.6, 7.1, 7.1 Hz), 3.67 (qq, 1H, J=6.8, 7.1 Hz), 3.69 (dd, 1H, J=4.6, 11.1 Hz), 3.78 (dd, 1H, J=7.1, 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.9, 22.9, 34.5, 50.4, 64.8, 203.5; IR (neat) 3414, 2969, 1679, 1454, 1054, 966 cm^{-1}; MS m/z 162 (M^+). Anal. calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70. Found: C, 51.76; H, 8.51; $[\alpha]_D^{27}$=−6.7 (c 0.19, EtOH) (23% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=100/1, flow rate=1.0 mL/min) assumed *R* isomer: t_R=37.1 min (major), assumed *S* isomer: t_R=41.8 min (minor).

4.3. Determination of absolute configurations

4.3.1. (*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylpropan-1-one (7). To a solution of **6** (142 mg, 0.542 mmol) in THF (2.2 mL) at −40°C was added a PhLi solution (1.06 M cyclohexane/ether sol., 0.61 mL, 0.650 mmol) over 10 min. The mixture was stirred for 10 min and quenched by addition of saturated NH_4Cl aqueous solution. Ether was then added, the layers were separated, and the aqueous phase was extracted with ether twice. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by silica gel chromatography (AcOEt/hexane 1/6) to provide **7** as a colorless oil (50.2 mg, 0.180 mmol, 33% yield) and **6** (95.1 mg, 0.364 mmol, 67% recovery): ^{1}H NMR ($CDCl_3$) δ −0.04 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.17 (d, 3H, J=6.6 Hz), 3.68 (dd, 1H, J=6.1, 9.0 Hz), 3.72 (ddq, 1H, J=6.1, 6.6, 6.6 Hz), 3.92 (dd, 1H, J=6.6, 9.0 Hz), 7.42–7.49 (m, 2H), 7.51–7.58 (m, 1H), 7.94–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.6, 14.2, 18.2, 25.8, 43.6, 66.0, 128.4, 128.5, 132.8, 137.3, 203.7; IR (neat) 2929, 2856, 1684, 1257, 1217, 1099, 837, 777 cm^{-1}; MS m/z 278 (M^+). Anal. calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 68.85; H, 9.27; $[\alpha]_D^{26}$=−31.9 (c 1.44, EtOH).

4.3.2. (*R*)-3-Hydroxy-2-methyl-1-phenylpropan-1-one (8). To a solution of **7** (26.1 mg, 0.0937 mmol) in THF (1.9 mL) was added hydrogen fluoride–pyridine complex at 0°C in several portions until a suitable amount of desired product appeared on TLC. After 20 min, the solution was diluted with ether and neutralized with saturated sodium hydrogen carbonate aqueous solution. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The product was purified by silica gel chromatography (AcOEt/hexane 1/2) to provide **8** as a colorless oil (6.5 mg, 0.0396 mmol, 42% yield) and **8** (15.1 mg, 0.0542 mmol, 58% recovery): ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3H, J=7.1 Hz), 2.35 (brs), 3.68 (ddq, 1H, J=4.3, 7.0, 7.1 Hz), 3.80 (dd, 1H, J=4.3, 11.1 Hz), 3.94 (dd, 1H, J=7.0, 11.1 Hz), 7.48 (dd, 2H, J=7.3, 8.5 Hz), 7.58 (t, 1H, J=7.3 Hz), 7.97 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.5, 42.9, 64.5, 128.4, 128.7, 133.3, 136.1, 204.4; IR (neat) 3415, 2936, 1681, 1448, 974, 704 cm^{-1}; MS m/z 164 (M^+). Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; N, 0.00. Found: C, 72.87; H, 7.40; N, 0.00; $[\alpha]_D^{24}$=−42.1 (c 0.28, EtOH) (>99% ee); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=19/1, flow rate=1.0 mL/min) *R* isomer: t_R=20.0 min (major), *S* isomer: t_R=17.2 min (minor).

4.3.3. 3-Hydroxy-2-methylpropionic acid methyl ester (10). To a solution of sodium methoxide (8.8 mg, 0.163 mmol) in MeOH (0.07 mL) was added **9** (51% ee, 18.2 mg, 0.103 mmol) at room temperature. The mixture was stirred for 100 min and quenched by addition of saturated NH_4Cl aqueous solution. Methylene chloride was then added, the layers were separated, and the aqueous phase was extracted with methylene chloride five times. The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure, and dried in vacuo to provide **10** as a colorless oil (8.1 mg, 0.0686 mmol, 67% yield): ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3H, J=7.3 Hz), 2.24 (brs), 2.62–2.76 (m, 1H), 3.66–3.78 (m, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.4, 41.6, 51.8, 64.6, 176.1; $[\alpha]_D^{17}$=−11.1 (c 0.41, MeOH).

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