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Reductive aldol cyclizations of unsaturated thioester derivatives of 1, 3-cyclopentanedione catalyzed by chiral copper hydrides

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ABSTRACT

The first study on the asymmetric reductive aldol reactions of enethioate derivatives of 1,3-cyclopentanedione showed that 5 mol % of TANIAPHOS (SL-T001-1), and $Cu(OAc)_2 \cdot H_2O$, together with phenylsilane as the stoichiometric reductant, generated the best yields and enantioselectivities of β-hydroxythioester products. With *S*-benzyl keto-enethioate as substrate, the bicyclo[4.3.0] hydroxythioester product was obtained only as the all-cis diastereomer, in good yield (84%) and enantioselectivity (up to 90% ee). With the related indanedione enethioate derivatives, the reductive aldol cyclization could attain up to 96% ee. These results demonstrate that enethioates have a significantly different reactivity and selectivity profile compared to enoate derivatives in the copper-catalyzed reductive aldol cyclization.

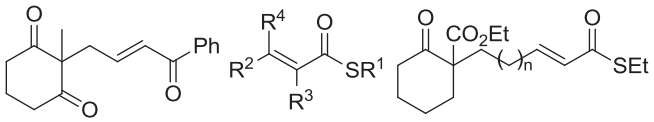
1. Introduction

Asymmetric domino reactions are powerful tools to construct optically enriched cyclic and polycyclic compounds.[1] The incorporation of domino reactions can confer tremendous efficiency and economy to a synthetic plan, which are particularly significant in order to simplify the synthesis of complex natural products.[2] The ability to execute asymmetric domino reactions in a catalytic manner further augments the utility and application of these reactions.[3]

We have had a long standing interest in reductive aldol reactions mediated by copper hydrides.[4] Especially in the context of intramolecular aldol reactions, the generation of enolates by conjugate reduction differentiates the roles of multiple carbonyl groups in the precursor, and obviates the need to synthesize preformed enolates by a separate step. This copper hydride-induced reductive aldol cyclization has already found application in a number of total syntheses of natural products, where conventional aldol reactions produced inferior results.[5]

In recent years, these domino reductive aldol cyclizations have been developed to achieve asymmetric induction.[6] Usefully, the intramolecular versions of these reactions can construct mono- and polycyclic compounds with several contiguous stereogenic centers and functional groups.[7]

We began our investigations in enantioselective reductive aldol cyclizations by desymmetrization in the context of enone derivatives of 1,3-diketones, such as **1** (Fig. 1).[8] However, after a series of screenings with various chiral ligands, the enantiomeric excesses obtained in the aldol reaction were rather dismal.



1 2 3

Fig. 1. Substrates for copper hydride catalyzed reductions.

Recently we have investigated the conjugate reduction of unsaturated thioesters.[9] Thioesters are versatile synthetic substrates and intermediates. They enolize more readily to react as nucleophiles,[10] and are also more activated for acylation;[11] under catalysis by palladium they can be reduced to aldehydes[12] or alkylated to yield ketones.[13] Compared with oxoesters, conjugate addition to the unsaturated thioester is also more facile.[14]

Therefore we were surprised that α,β-unsaturated thioesters **2** were initially rather resistant to copper-catalyzed conjugate reduction (Fig. 1). Finally, the use of ligands, such as bis(diphenylphosphino)ferrocene (dppf) and bis(diphenylphosphino)benzene (BDP) produced copper hydrides, which were significantly more reactive, and catalyzed the conjugate reduction effectively in the presence of PMHS as the stoichiometric reductant. Under similar

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conditions, reductive aldol cyclization of keto-enethioates, such as **3** (n=0, 1; Fig. 1) could also be effected.[9]

Encouraged by these results, we proceeded to investigate the catalytic enantioselective reductive aldol reactions of thioester derivatives. Herein we report the first examples of desymmetrizing reductive aldol cyclizations of keto-enethioates to produce bicyclic hydroxythioesters in good yield and diastereoselectivity, and with up to 96% ee.

2. Results and discussion

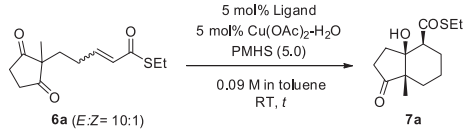
2.1. Preparation of substrates 6

To investigate the desymmetrizing reductive aldol cyclization, a family of *meso* unsaturated thioester substrates **6** were synthesized. Reaction of 2-methyl-1,3-cyclopentanedione with acrolein yielded aldehyde **4a**, which was subjected to Wittig reactions with each of **5a**–**e**[15] to yield a series of thioesters **6a**–**e** for the investigations. Similarly, the Wittig reaction of indanediones **4b**–**c** yielded enethioates **6f**–**g** (Scheme 1).

The unsaturated thioesters **6** were generally obtained as a 7–10:1 mixture of *E*:*Z* isomers, except for **6b**, which was a 2.7:1 *E*/*Z* mixture, and **6f**–**g**, which were found exclusively in the (*E*)-form. In the cases where *E*/*Z* isomeric mixtures of **6** were obtained, the isomers were unfortunately inseparable by flash chromatography. An attempt to obtain pure (*E*)-isomer by treatment of the mixture of **6a** isomers with a catalytic amount of DMAP resulted in only a 34% yield of pure (*E*)-**6a**.[14] It appeared that, in addition to promoting the equilibration of (*Z*)-**6a** to (*E*)-**6a**, DMAP also induced other side reactions. Therefore this first study on reductive aldol cyclizations were carried out in some cases with isomeric mixtures of **6**, predominantly in the (*E*)-form (Scheme 1).

overnight. Many other products appeared to have been generated under these reaction conditions.

Table 1
Screening of ligands for reductive aldol cyclization of **6a**

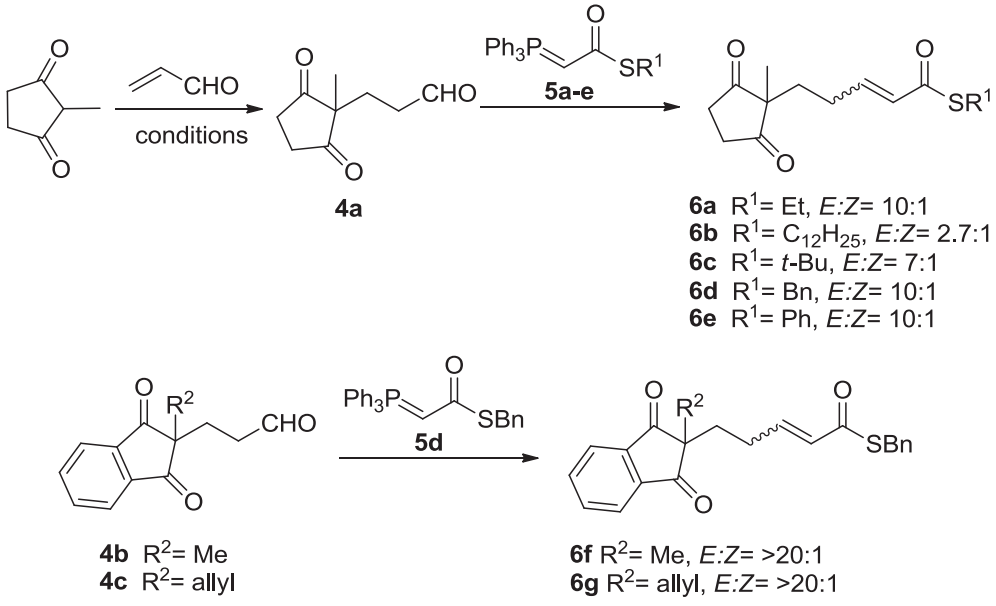


6a (*E*:*Z*= 10:1) **7a**

Entry	Ligand	t (h)	Isolated yield	dr	% ee[a]
1[b]	BDP[c]	12	16%	64:36	—
2	(*R*)-BINAP	12	43%	93:7	18
3	(*R*)-*p*-*tol*—BINAP	12	26%	88:12	26
4	(*R*)-MeO—BIPHEP	12	16%	75:25	4
5	(*R*)-BINAPHANE	72	22%	92:8	2
6	JosiPhos (SL-J001-1)	48	43%	98:2	17
7	TaniaPhos (SL-T001-1)	72	72%	>98:2	79
8	MandyPhos (SL-M001-1)	72	51%	98:2	24
9	WalPhos (SL-W001-1)	72	60%	>98:2	56

[a] Enantiomeric excesses were determined by HPLC using a Chiralcel AD-3 chiral column.
[b] $Cu(OAc)_2 \cdot H_2O$ (10 mol %) was used.
[c] BDP (10 mol %) was used.

Biphenyl or binapthyl chiral ligands, such as (*R*)-*p*-*tol*—BINAP, (*R*)-MeO—BIPHEP, and (*R*)-BINAPHANE produced copper hydrides that mediated the reductive aldol reaction without any significant increase in yields, although the diastereoselectivity was improved (Table 1, entries 3–5). Of these, (*R*)-BINAP was the most effective, and the yield and dr improved to 43% and 93:7, respectively. The enantioselectivity, however, was low (Table 1, entry 2). Bisphos-



Scheme 1. Synthesis of enethioates **6a**–**g**.

2.2. Enantioselective reductive aldol cyclization of 6a

The reductive aldol cyclization catalyzed by copper hydrides was first investigated using **6a** as substrate (Table 1). Using 10 mol % of each of $Cu(OAc)_2 \cdot H_2O$ and BDP, 5 hydride equivalents of PMHS, which are the conditions that had been used for the copper-catalyzed reductive aldol reactions of **3**,[9] the reaction of **6a** disappointingly yielded a 64:36 diastereomeric mixture of aldol products, in only 16% yield after reaction at room temperature

phine ligands based on the ferrocene skeleton, such as JosiPhos, TaniaPhos, MandyPhos, and WalPhos were also screened. All of these ligands formed copper hydrides that induced the reductive aldol reaction with better yields and greatly improved diastereoselectivity. In particular, the use of TaniaPhos (SL-T001-1) generated **7a** bearing three functional groups and three contiguous stereocenters, as the only diastereomer observed. The highest yield and enantioselectivity attained so far was 72% yield and 79% ee, respectively (Table 1, entry 7).

2.3. Structure determination of 7a

The structure of the major product is assigned as **7a**, in which the methyl, hydroxyl, and thioester groups are all in cis relative to each other. The stereochemistry of **7a** was deduced based on 2D-NMR (H-H NOESY, COSY) spectral analysis, as shown in Fig. 2.[16] The relative stereochemistry was suggested by the NOE correlations of H4 (whose coupling constant J=11.9 Hz indicated that it was axial) to $H6_a$, and $H2_a$.The absence of any NOE between the methyl group and H4, and the NOE correlation of the methyl moiety with both the axial and equatorial protons of C7 were indicative of the methyl group adopting an equatorial position.

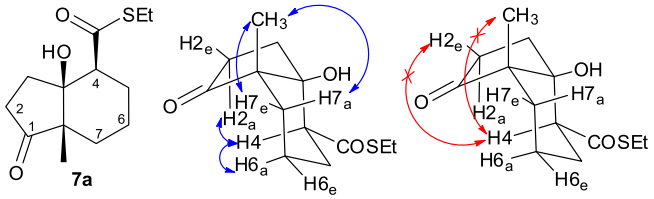


Fig. 2. Structure elucidation of **7a** by 2D-NOE correlations.

The related reductive aldol product (±)-**7c** (vide infra) is a crystalline compound, and its relative stereochemistry was also determined by X-ray crystallography (Fig. 3).[17] The stereochemistry was found to be the same as that of **7a**.

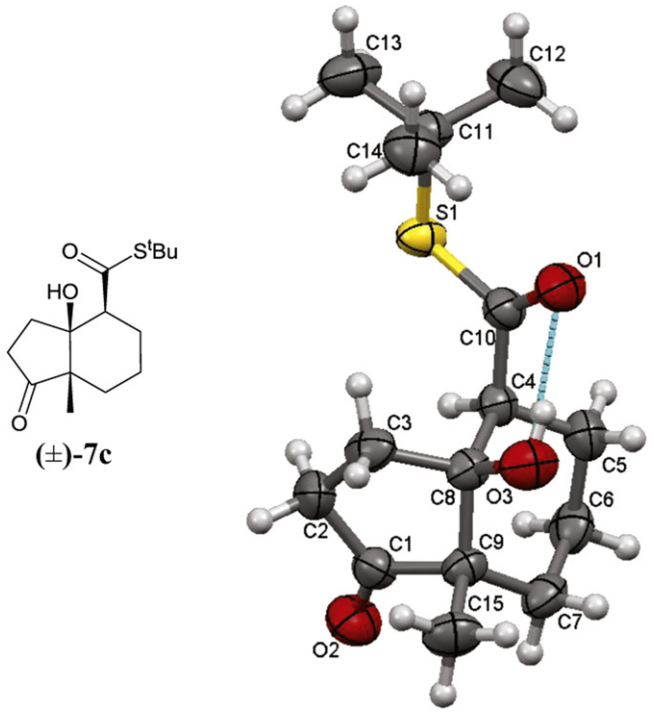
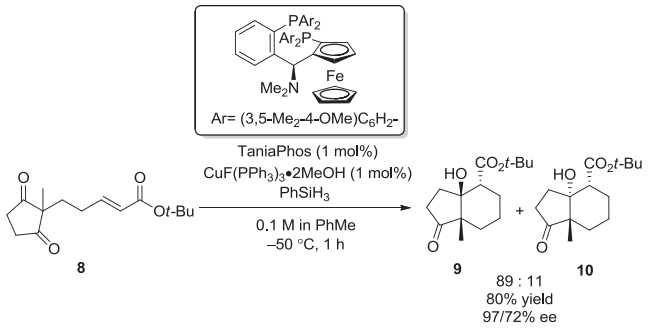


Fig. 3. ORTEP of (±)-**7c**.

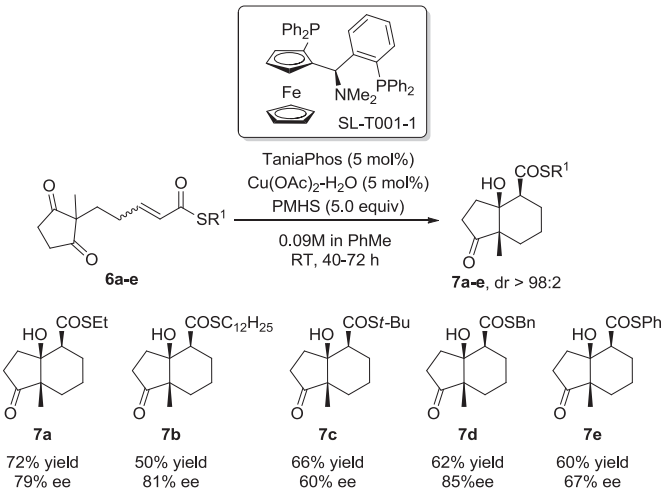
Notably, and in contrast, the relative stereochemistry of the major product **9** obtained from the enantioselective reduction of the analogous enoate derivative **8** possessed the alternative relative stereochemistry of a trans-relationship between the hydroxyl group and the oxoester (Scheme 2).[7a]

2.4. Optimizations of the enethioate substrate 6

With the optimized ligand in hand, we further explored the effect of the particular mercaptan (R^1) from which the thioester is derived, on the selectivity of the reductive aldol reaction. As shown in Scheme 3, unsaturated thioesters **6b**–**e** were subjected to reaction under the optimized conditions in the presence of 5 mol % of copper and the TaniaPhos ligand. In all cases, the all-cis diastereomers **7b**–**d** were the only aldol products observed. The reductive cyclization yields were moderate to good. When R^1=*t*-Bu, the increase in steric hindrance did not improve the enantioselectivity and rather resulted in a loss of ee. Similarly, the thioester (**6e**) derived from thiophenol also reacted to generate **7e** with lower enantioselectivity. However, the thioester **6d** in which R^1=Bn resulted in an improvement in the reductive cyclization to give **7d** in 85% ee and 62% yield.



Scheme 2. Reductive cyclization of enoate **8**.[7a]

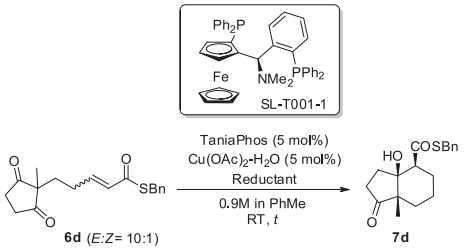


Scheme 3. Optimizations of R^1 in enethioates **7**.

2.5. Optimizations of the reductant

With the optimized thioester in hand, the effect of the reductant on the reaction was investigated. The most used stoichiometric reducing agents in copper-mediated reductions are silanes, to take advantage of the strong Si–O bond formation that concomitantly promotes copper hydride regeneration. The results are summarized in Table 2. The identity of the silane did not have any significant effect on the dr or the ee of the reaction. However, the activity of the silane affected the yields and the time required for complete reaction. The most effective silane was $PhSiH_3$, which generated the highest yield of product and in the shortest reaction time of 4 h (Table 2, entry 1), while $PhMe_2SiH$ did not seem to be able to promote copper hydride regeneration at all (Table 2, entry 3). We also examined pinacolborane as a reductant, and while the reductive aldol reaction proceeded, both the yield and the ee of **7d** were inferior to the those obtained using phenylsilane. The use of

Table 2
Screening of reductants



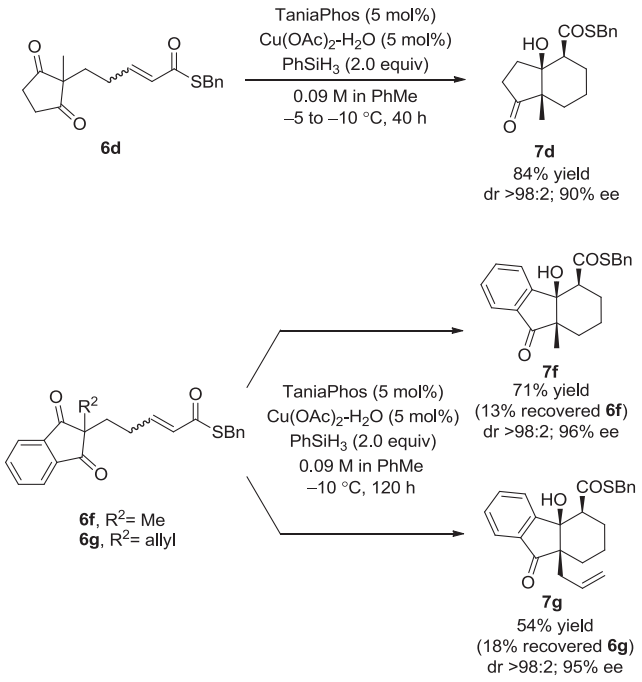
Entry	Reductant	t (h)	Isolated Yield of **7d**	dr	ee (%)[a]
1	$PhSiH_3$	4	83%	>98:2	84
2	Ph_2SiH_2	16	82%	>98:2	83
3	$PhMe_2SiH$	48	nr	—	—
4	$(EtO)_2MeSiH$	48	71%	>98:2	84
5	Pinacolborane	16	74%	>98:2	75
6[b]	$PhSiH_3$	4	74%	>98:2	86

[a] Determined by HPLC on CHIRACEL AY-3 column.
[b] $CuF(PPh_3)_3$ (5 mol %) was used.

an alternative, air-stable copper (I) source, tris(triphenylphosphine) copper fluoride with phenylsilane was also an effective combination, in which the ee of **7d** was similar, but the yield was reduced by about 10%.

2.6. Optimization of temperature

Due to the significant decrease of reaction time employing phenylsilane as reductant, we could then investigate the outcome of the reductive aldol reaction at lower temperatures, which was expected to increase the reaction time, but should result in improved enantioselectivity. When the reduction of **6d** was conducted at −5 to−10 °C with 5 mol % of TaniaPhos and $Cu(OAc)_2 \cdot H_2O$ in the presence of phenylsilane, bicyclic **7d** was obtained in 84% yield and 90% ee after reaction for 40 h (Scheme 4).



Scheme 4. Reductive cyclization of **6d**,**f**,**g** at −10 °C.

These results (Scheme 4) stand in contrast with the copper-catalyzed reductive cyclization of oxoester derivative **8** (Scheme 2).[7a] Although the optimized conditions for enantioselective reductive aldol reaction of **6** and **8** have been found to be rather similar, enoate **8** was much more reactive, requiring only 2 h for complete reaction at −50 °C, and achieved a higher enantioselectivity (Scheme 2). On the other hand, a higher diastereoselectivity was observed in the reduction of enethioate **6d**; moreover, the major aldol product was of a different relative stereochemistry.

We have also applied the optimized reductive conditions to the aldol reactions of indanediones **6f** and **6g**, which resulted in incomplete reaction after 120 h, but achieved higher enantioselectivities (96% ee and 95% ee, respectively) in the polycyclic products **7f** and **7g** (Scheme 4).

3. Conclusions

In this study, the reductive adol cyclizations of keto-enethioate derivatives of 1,3-cyclopentanedione and the related 1,3-indanedione have been examined for the first time. Copper catalysis with TaniaPhos (SL-T001-1) as ligand induced the reductive aldol cyclization of **6d** to produce *cis*-fused perhydroindane **7d** as a single diastereomer, in good yield and in up to 90% ee. The reductive aldol cyclization of **6f** produced **7f** also as a single diastereomer, with an even higher 96% ee. The reaction potential and versatility afforded by thioester group could allow ready access to other related, optically active intermediates from **7d** or **7f**. The differences in the reactivity and selectivity of this system compared to its enoate counterpart merits additional investigation. The substrate scope of this methodology and further optimizations of this reaction type are currently under way.

4. Experimental

4.1. General methods

All ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$), with tetramethylsilane (TMS) as an internal standard at ambient temperature on a Bruker DPX 400, or 500 MHz Fourier Transform Spectrometer operating at 400 MHz, or 500 MHz for ^1H, and at 100 MHz, or 125 MHz, respectively for ^{13}C. All the spectra were calibrated at δ 7.26 ppm for ^1H and δ 77.03 ppm for ^{13}C. Spectral features are designated as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=mutiplet, and br=broad. IR absorption spectra were recorded as a solution in CH_2Cl_2 on a Bio-Rad FT 165 Spectrophotometer from 4000 cm^{-1} to 400 cm^{-1}. Mass spectra were obtained on a Finnigan MAT 95 mass spectrometer or API QSTAR PULSAR LC/MS/TOF System for both low resolution and high resolution, with accurate mass reported for the molecular ion (M^+) or the next largest fragment thereof. Analytical HPLC was carried out on Waters HPLC systems equipped with a 1525 Binary HPLC Pump, Waters 2707 autosampler and a Waters 2489 variable wavelength UV−vis detector or Waters 2998 PDA detector, operated using Breeze2 software. Optical rotations were obtained with a Perkin−Elmer polarimeter operating at 589 nm, using CH_2Cl_2 as solvent. X-ray crystallographic data was collected on a Bruker Apex II CCD detector with graphite monochromated Mo Kα radiation.

HPLC grade CH_2Cl_2 was used as received. PhMe was distilled from CaH_2 under argon.

4.2. General procedure for the preparation of keto-enethioates 6a−g

Phosphoranes **5a** (R^1=Et), **5b** (R^1=C_12H_{25}), **5c** (R^1=*t*-Bu), **5d** (R^1=Bn), **5e** (R^1=Ph), were prepared from the corresponding *S*-

alkyl 2-bromoethanethioates and triphenylphosphine, according to literature procedures.[18]

To a solution of aldehyde **4** (1.0 equiv) in CH_2Cl_2 was added the corresponding phosphorane **5a**–**e** (1.2 equiv). The reaction mixture was stirred at room temperature for 12 h. The solvent was removed by rotoevaporation, and the residue was subjected to flash chromatography on silica gel to give the corresponding enethioates **6a**–**g** as mixture of (*E*)- and (*Z*)-isomers.

*4.2.1. Synthesis of **6a**.* According to the general procedure in Section 4.2, aldehyde **4a**[19] (1.66 g, 9.87 mmol) was treated with phosphorane **5a** (4.30 g, 12.0 mmol) in CH_2Cl_2 (30 mL). After purification by chromatography, **6a** (2.52 g, 98% yield, *E*/*Z*=10:1) was obtained as a yellow oil: R_f (25% EtOAc in hexane): 0.22; IR (CH_2Cl_2): 3053, 1724 (C=O, cyclopentanone), 1670 (unsaturated C=O, thioester), 1635 (C=C) cm^{-1}; (*E*)-**6a**, ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (dt, *J*=15.6, 8.3 Hz, 1H), 6.03 (d, *J*=15.6 Hz, 1H), 2.92 (q, *J*=7.3 Hz, 2H), 2.85–2.62 (m, 4H), 2.11–2.08 (m, 2H), 1.84–1.80 (m, 2H), 1.27 (t, *J*=7.8 Hz, 1H), 1.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9, 189.8, 144.1, 129.5, 56.1, 35.2, 32.6, 27.3, 23.2, 20.2, 14.8 ppm. LRMS (EI, 20 eV): *m*/*z* 254.1 (M^+, 1), 193.1 ($M^+-SC_2H_5$, 26), 165.1 ($M^+-COSC_2H_5$, 4); HRMS (EI, 20 eV): calcd for $C_{13}H_{18}O_3S$ (M^+), 254.0971, found 254.0964.

*4.2.2. Synthesis of **6b**.* According to the general procedure in Section 4.2, aldehyde **4a**[19] (0.95 g, 5.6 mmol) was treated with phosphorane **5b** (3.5 g, 6.9 mmol) in CH_2Cl_2 (40 mL). After purification by chromatography, **6b** (0.51 g, 23% yield, *E*/*Z*=2.7:1) was obtained as yellow oil: R_f (25% EtOAc in hexane): 0.30; IR (CH_2Cl_2): 3051, 1724 (C=O, ketone), 1683 (C=O, thioester), 1635 (C=C) cm^{-1}; (*E*)-**6b**: ^1H NMR (400 MHz, $CDCl_3$): 6.70 (dt, *J*=15.4, 6.9 Hz, 1H), 6.03 (d, *J*=15.5 Hz, 1H), 2.94–2.74 (m, 6H), 2.11–2.09 (m, 2H), 1.85–1.80 (m, 2H), 1.58–1.55 (m, 3H), 1.32–1.25 (m, 18H), 1.15 (s, 3H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 205.2, 77.8, 56.3, 53.7, 34.5, 31.9, 30.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 28.8, 28.3, 26.0, 22.7, 22.5, 19.1, 14.1 ppm; LRMS (EI, 20 eV): *m*/*z* 394.2 (M^+, 5), 193.1 ($M^+-SC_{12}H_{25}$, 24), 165.1 ($M^+-COSC_{12}H_{25}$, 25); HRMS (EI, 20 eV): calcd for $C_{23}H_{38}O_3S$ (M^+), 394.2536, found 394.2534.

*4.2.3. Synthesis of **6c**.* According to the general procedure in Section 4.2, aldehyde **4a**[19] (0.95 g, 5.6 mmol) was treated with reagent **5c** (2.79 g, 7.1 mmol) in CH_2Cl_2 (35 mL). After purification by chromatography, **6c** (1.16 g, 73% yield, *E*/*Z*=7:1) was obtained as white solid. Melting point 66–70 °C R_f (25% EtOAc in hexane): 0.25; IR (CH_2Cl_2): 3051, 2968, 1722 (C=O, ketone), 1652 (C=O, unsaturated thioester), 1627 (C=C) cm^{-1}; (*E*)-**6c**: ^1H NMR (400 MHz, $CDCl_3$): 6.62 (dt, *J*=15.5, 6.9 Hz, 1H), 5.92 (d, *J*=15.5 Hz, 1H), 2.85–2.69 (m, 4H), 2.07–2.03 (m, 2H), 1.83–1.79 (m, 2H), 1.48 (s, 9H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9, 190.4, 141.7, 130.2, 56.1, 48.1, 35.0, 34.9, 32.8, 29.9, 27.2, 20.0 ppm; LRMS (EI, 20 eV): *m*/*z* 282.1 (M^+, 1), 193.1 ($M^+-SC_4H_9$, 26), 165.1 ($M^+-COSC_4H_9$, 3); HRMS (EI, 20 eV): calcd for $C_{15}H_{22}O_3S$ (M^+), 282.1284, found 282.1283.

*4.2.4. Synthesis of **6d**.* According to the general procedure in Section 4.2, aldehyde **4a**[19] (1.71 g, 10.2 mmol) was treated with phosphorane **5d** (5.20 g, 6.2 mmol) in CH_2Cl_2 (35 mL). After purification by chromatography, **6d** (2.33 g, 72% yield, *E*/*Z*=10:1) was obtained as yellow solid: R_f (25% EtOAc in hexane): 0.24; mp=58–61 °C; IR (CH_2Cl_2): 3053, 2976, 1722 (C=O, ketone), 1668 (C=O, unsaturated thioester), 1633 (C=C) cm^{-1}; (*E*)-**6d**: ^1H NMR (400 MHz, $CDCl_3$): 7.30–7.22 (m, 5H), 6.74 (dt, *J*=15.5, 6.9 Hz, 1H), 6.04 (d, *J*=15.5 Hz, 1H), 4.17 (s, 2H), 2.84–2.67 (m, 4H), 2.10–2.06 (m, 2H), 1.83–1.59 (m, 2H), 1.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.8, 188.9, 143.6, 137.5, 129.0, 128.9, 128.6, 127.3, 56.1, 35.2, 34.9, 32.9, 32.5, 27.3, 20.1 ppm; LRMS (EI, 20 eV): *m*/*z* 316.2 (M^+, 7), 193.1 ($M^+-SC_7H_7$, 23), 165.1 ($M^+-COSC_7H_7$, 12); HRMS (EI, 20 eV): calcd for $C_{18}H_{20}O_3S$ (M^+), 316.1128, found 316.1128.

*4.2.5. Synthesis of **6e**.* According to the general procedure in Section 4.2, aldehyde **4a**[19] (0.95 g, 5.6 mmol) was treated with **5e** (2.8 g, 6.8 mmol) in CH_2Cl_2 (40 mL). After purification by chromatography, **6e** (0.31 g, 18% yield, *E*/*Z*=10:1) was obtained as yellow solid: R_f (25% EtOAc in hexane): 0.32; mp=49–51 °C; IR (CH_2Cl_2): 3051, 2927, 2856, 2360, 2337, 1722 (C=O, ketone), 1668 (C=O, thioester), 1633 (C=C) cm^{-1}; (*E*)-**6e**: ^1H NMR (400 MHz, $CDCl_3$): 7.44–7.40 (m, 5H), 6.80 (dt, *J*=15.4, 6.9 Hz, 1H), 6.12 (d, *J*=15.5 Hz, 1H), 2.87–2.71 (m, 4H), 2.15–2.12 (m, 2H), 1.86–1.82 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 215.7, 187.7, 146.0, 144.4, 134.6, 134.5, 133.2, 129.4, 129.2, 128.6, 127.3, 126.1, 56.1, 35.1, 35.0, 33.8, 32.5, 32.0, 27.3, 25.4, 20.1, 19.9 ppm; LRMS (EI, 20 eV): *m*/*z* 302.1 (M^+, 0.8), 193.1 ($M^+-SC_6H_5$, 35), 165.1 ($M^+-COSC_6H_5$, 5); HRMS (EI, 20 eV): calcd for $C_{17}H_{18}O_3S$ (M^+), 302.0971, found 302.0972.

*4.2.6. Synthesis of **6f**.* According to the general procedure in Section 4.2, aldehyde **4b**[20] (0.24 g, 1.5 mmol) was treated with **5d** (1.0 g, 2.3 mmol) in CH_2Cl_2 (40 mL). After purification by chromatography, **6f** (0.11 g, 20% yield, *E*/*Z*=100:0) was obtained as an orange oil: R_f (25% EtOAc in hexane): 0.40; IR (CH_2Cl_2): 3055, 2932, 2870, 1705 (C=O, ketone), 1674 (C=O, unsaturated thioester), 1628 (C=C), 1597 cm^{-1}; (*E*)-**6f**: ^1H NMR (400 MHz, $CDCl_3$): 7.96–7.94 (m, 2H), 7.84–7.81 (m, 2H), 7.29–7.22 (m, 5H), 6.71 (dt, *J*=15.5, 6.4 Hz, 1H), 5.88 (dt, *J*=15.5, 1.5 Hz, 1H), 4.13 (s, 2H), 2.06–1.97 (m, 4H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 203.8, 188.8, 143.6, 141.1, 137.6, 135.9, 135.8, 128.8, 128.5, 127.2, 123.4, 53.3, 33.1, 32.8, 27.7, 25.6, 19.9 ppm; LRMS (ESI, 3 kV): *m*/*z* 365 ($M+H^+$); HRMS (ESI, 3 kV): calcd for $C_{22}H_{20}O_3S$ ($M+H^+$) 365.1206, found 365.1200.

*4.2.7. Synthesis of **6g**.* According to the general procedure in Section 4.2, aldehyde **4c** (2.42 g, 10.0 mmol) was treated with **5d** (4.60 g, 11.0 mmol) in CH_2Cl_2 (40 mL). After purification by chromatography, **6g** (1 g, 26% yield, *E*/*Z*=100:0) was obtained as yellow oil: R_f (25% EtOAc in hexane): 0.45; IR (CH_2Cl_2): 3063, 2994, 2090, 1735 (C=O, ketone), 1712 (C=O, unsaturated thioester), 1566 cm^{-1}; (*E*)-**6g**: ^1H NMR (400 MHz, $CDCl_3$): 7.95–7.93 (m, 2H), 7.82–7.80 (m, 2H), 7.29–7.26 (m, 5H), 6.71–6.67 (m, 1H), 5.86 (d, *J*=15.5 Hz, 1H), 6.12 (d, *J*=15.5 Hz, 1H), 5.45 (ddt, *J*=17.4, 10.1, 7.5 Hz, 1H), 5.03 (dd, *J*=16.9, 1.5 Hz, 1H), 4.90 (dd, *J*=10.2, 1.6 Hz, 1H), 4.13 (s, 2H), 2.52 (d, *J*=7.5 Hz, 2H), 2.01–1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 203.3, 188.8, 143.5, 142.1, 137.6, 135.9, 131.1, 128.9, 128.6, 127.2, 123.1, 119.8, 57.7, 39.5, 32.9, 32.3, 27.6 ppm; LRMS (EI, 20 eV): *m*/*z* 390.1 (M^+, 0.9), 268.1 ($M^+-SC_7H_7$, 3.5), 239.1 ($M^+-COSC_7H_7$, 5); HRMS (EI, 20 eV): calcd for $C_{24}H_{22}O_3S$ (M^+), 390.1290, found 390.1284.

4.3. General procedure for asymmetric reductive aldol cyclization of 6a–g

$Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol), TaniaPhos (SL-T001-1, 5.0 mg, 0.0075 mmol) were transferred into an oven-dried 5 mL round-bottomed flask, to which anhydrous PhMe (1.0 mL) and silane (0.75 mmol) were added under argon. The reaction mixture was stirred at room temperature until a characteristic greenish-yellow color was observed. The reaction mixture was cooled to the target reaction temperature. Substrate **6** (0.15 mmol) in PhMe (1.0 mL) was added to the reaction mixture via cannula. The progress of the reaction was monitored by TLC. The reaction was quenched by the addition of 1 M HCl (1.0 mL). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (3×5 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography of the

residue on silica gel using 5%–20% EtOAc in hexane afforded aldol product **7**.

The corresponding reductive aldol reactions to obtain racemic products were similarly executed, but using either BDP or dppf as achiral ligands.

*4.3.1. Asymmetric reductive aldol cyclization of **6a**.* According to the general procedure in Section 4.3, TaniaPhos (10 mg, 0.015 mmol), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol), and PMHS (95 μL, 1.5 mmol) in 2.3 mL PhMe was treated with **6a** (77 mg, 0.30 mmol) dissolved in PhMe (2×0.3 mL) at room temperature for 72 h. After workup and chromatographic purification, **7a** was obtained as a colorless oil (55 mg, 72% yield, 79% ee). Compound **7a**: $[\alpha]_D^{20}$ −71.2 (*c* 1); DAICEL CHIRALCEL AD-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 18.44 min (minor), 19.104 min (major); R_f (25% EtOAc in hexane): 0.50; IR (CH_2Cl_2): 3053, 2974, 2939, 2932, 1739 (C=O, cyclopentanone), 1652 (C=O, thioester) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.36 (s, 1H), 2.91 (q, *J*=7.4 Hz, 2H), 2.56 (ddd, *J*=19.6, 10.4, 2.1 Hz, 1H), 2.37 (dd, *J*=11.9, 3.4 Hz, 1H), 2.25 (ddd, *J*=19.7, 9.6, 9.5 Hz, 1H), 2.13 (dt, *J*=13.1, 10.5 Hz, 1H), 2.03 (ddd, *J*=11.7, 9.5, 1.9 Hz, 1H), 1.89 (dm, *J*=13.9 Hz, 1H), 1.82 (dtd, *J*=12.7, 12.5, 3.3 Hz, 1H), 1.71 (dm, *J*=12.4 Hz, 1H), 1.64–1.61 (m, 1H), 1.37 (ddd, *J*=13.7, 13.3, 4.5 Hz, 1H), 1.32 (t, *J*=7.3 Hz, 3H), 1.21 (dtt, *J*=13.2, 13.1, 3.7 Hz, 1H), 1.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 205.2, 77.9, 56.8, 53.7, 34.5, 30.8, 28.3, 25.9, 23.6, 22.5, 19.1, 14.5 ppm; LRMS (EI, 20 eV): *m*/*z* 256.1 (M^+, 7), 195.1 ($M^+-SC_2H_5$, 17), 167.1 ($M^+-COSC_2H_5$, 72); HRMS (EI, 20 eV): calcd for $C_{13}H_{20}O_3S$ (M^+), 256.1128; found 256.1126.

*4.3.2. Asymmetric reductive aldol cyclization of **6b**.* According to the general procedure in Section 4.3, TaniaPhos (5.0 mg, 0.0075 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol), and PMHS (50 μL, 0.75 mmol) in 1 mL PhMe was treated with **6b** (60 mg, 0.15 mmol) dissolved in PhMe (2×0.3 mL) at room temperature for 60 h. After workup and chromatographic purification, **7b** was obtained as a colorless oil (30 mg, 50% yield, 81% ee). Compound **7b**: $[\alpha]_D^{20}$ −37.5 (*c* 1); DAICEL CHIRALCEL AS-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 9.41 min (minor), 15.44 min (major); R_f (25% EtOAc in hexane): 0.47; IR (CH_2Cl_2): 3053, 2927, 2852, 1733 (C=O, ketone), 1652 (C=O, thioester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.37 (br s, 1H), 2.91 (td, *J*=7.2, 2.0 Hz, 2H), 2.56 (ddd, *J*=19.7, 10.4, 2.1 Hz, 1H), 2.37 (dd, *J*=11.9, 3.4 Hz, 1H), 2.25 (ddd, *J*=19.4, 9.6, 9.5 Hz, 1H), 2.13 (dt, *J*=13.1, 10.1 Hz, 1H), 2.01 (ddd, *J*=15.0, 9.5, 1.9 Hz, 1H),1.90 (dm, *J*=13.9 Hz, 1H), 1.81 (dtd, *J*=12.5, 12.4, 3.2 Hz, 1H), 1.70 (dm, *J*=13.0 Hz, 1H), 1.70–1.61 (m, 4H), 1.59–1.14 (m, 23H), 1.02 (s, 3H), 0.88 (t, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 205.2, 77.9, 56.3, 53.7, 34.5, 31.9, 30.8, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 28.8, 28.3, 26.0, 22.7, 22.6, 19.1, 14.1 ppm; LRMS (EI, 20 eV): *m*/*z* 396.2 (M^+, 7), 195.1 ($M^+-SC_{12}H_{25}$, 16), 167.1 ($M^+-COSC_{12}H_{25}$, 100); HRMS (EI, 20 eV): calcd for $C_{23}H_{40}O_3S$ (M^+), 396.2693, found 396.2709.

*4.3.3. Asymmetric reductive aldol cyclization of **6c**.* According to the general procedure in Section 4.3, TaniaPhos (5.0 mg, 0.0075 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol), and PMHS (50 μL, 0.75 mmol) in 1.0 mL PhMe was treated with **6c** (42.4 mg, 0.15 mmol) dissolved in PhMe (2×0.3 mL) at room temperature for 44 h. After workup and chromatographic purification, **7c** (27.9 mg, 66% yield, 60% ee) was obtained as a white solid; mp=69–71 °C; $[\alpha]_D^{20}$ −33.5 (*c* 0.27); DAICEL CHIRALCEL AD-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 11.723 min (minor), 13.232 min (major); R_f (25% EtOAc in hexane): 0.45; IR (CH_2Cl_2): 3053, 1733 (C=O, ketone), 1652 (C=O, thioester) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.48 (s, 1H), 2.55 (ddd, *J*=19.7, 10.2, 2.2 Hz, 1H), 2.28–2.20 (m, 2H), 2.16–2.03 (m, 2H), 1.89 (dm, *J*=13.8 Hz, 1H), 1.79 (dtd, *J*=12.6, 12.5, 3.3 Hz, 1H), 1.69–1.64 (m, 1H), 1.63–1.52 (m, 1H), 1.48 (s, 9H), 1.36 (ddd, *J*=13.6, 13.5, 4.6 Hz, 1H), 1.14 (dtt, 13.3, 13.2, 3.8 Hz, 1H), 1.00 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.9, 206.2, 78.0, 56.0, 49.2, 34.6, 30.8, 29.6, 28.3, 25.8, 22.6, 19.1 ppm. LRMS (EI, 20 eV): *m*/*z* 284.1 (M^+, 3), 195.1 ($M^+-SC_4H_9$, 59), 167.1 ($M^+-COSC_4H_9$, 98); HRMS (EI, 20 eV): calcd for $C_{15}H_{24}O_3S$ (M^+), 284.1441, found 284.1438.

*4.3.4. Asymmetric reductive aldol cyclization of **6d**.* According to the general procedure in Section 4.3, Taniaphos (5.0 mg, 0.0075 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol), and $PhSiH_3$ (38 μL, 0.3 mmol) in 1.0 mL PhMe at −10 °C was treated with **6d** (47.4 mg, 0.15 mmol) in PhMe (2×0.3 mL) and stirred at −10 °C for 72 h. After workup and chromatographic purification, **7d** was obtained as a colorless oil (40.1 mg, 84% yield, 90% ee); $[\alpha]_D^{20}$ −58.7 (*c* 1); DAICEL CHIRALCEL AY-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 30.890 min (major), 38.272 min (minor); R_f (25% EtOAc in hexane): 0.40; IR (CH_2Cl_2): 3053, 1739 (C=O, cyclopentanone), 1652 (C=O, thioester) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 4.27 (br s, 1H), 4.18 (d, *J*=13.9 Hz, 1H), 4.14 (d, *J*=13.9 Hz, 1H), 2.55 (ddd, *J*=19.7, 10.3, 2.4 Hz, 1H), 2.39 (dd, *J*=11.9, 3.4 Hz, 1H), 2.23 (ddd, *J*=19.2, 10.0, 9.6 Hz, 1H), 2.11 (dt, *J*=13.5, 10.1 Hz, 1H), 2.00 (ddd, *J*=13.2, 9.3, 1.9 Hz, 1H), 1.90 (dm, *J*=13.9 Hz, 1H), 1.83 (dtd, *J*=12.7, 12.5, 3.4 Hz, 1H), 1.72 (dm, *J*=13.0 Hz, 1H), 1.71–1.60 (m, 1H), 1.37 (ddd, *J*=13.6, 13.3, 4.5 Hz, 1H), 1.19 (dtt, *J*=13.3, 13.0, 3.8 Hz, 1H), 1.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.7, 204.2, 136.6, 128.8, 128.7, 127.6, 77.9, 56.2, 53.8, 34.5, 33.5, 30.9, 28.3, 26.0, 22.5, 19.1 ppm; LRMS (EI, 20 eV): *m*/*z* 318.2 (M^+, 3), 195.1 ($M^+-SC_7H_7$, 5), 167.1 ($M^+-COSC_7H_7$, 18); HRMS (EI, 20 eV): calcd for $C_{18}H_{22}O_3S$ (M^+), 318.1284, found 318.1285.

*4.3.5. Asymmetric reductive aldol cyclization of **6e**.* According to the general procedure in Section 4.3, Taniaphos (5.0 mg, 0.0075 mmol), $Cu(OAc)_2-H_2O$ (1.5 mg, 0.0075 mmol), and PMHS (30 μL, 0.75 mmol) in 1.0 mL PhMe was treated with **6e** (48.0 mg, 0.16 mmol) in PhMe (2×0.3 mL) at room temperature for 40 h. After workup and chromatographic purification, **7e** was obtained as a colorless oil (29.3 mg, 60% yield, 67% ee); $[\alpha]_D^{20}$ −74.3 (*c* 0.67); DAICEL CHIRALCEL AY-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 35.436 min (major), 41.772 min (minor); R_f (25% EtOAc in hexane): 0.42; IR (CH_2Cl_2): 3159, 2252, 1739 (C=O, cyclopentanone), 1670 (C=O, thioester) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.48–7.40 (m, 5H), 4.15 (br s, 1H), 2.61 (ddd, *J*=19.7, 10.0, 3.0 Hz, 1H), 2.52 (dd, *J*=9.5, 5.3 Hz, 1H), 2.31 (ddd, *J*=19.6, 9.6, 9.5 Hz, 1H), 2.20–2.04 (m, 2H), 1.91 (dm, *J*=13.2 Hz, 1H), 1.88–1.855 (m, 2H), 1.71–1.65 (m, 1H), 1.38 (ddd, *J*=13.6, 13.1, 4.4 Hz, 1H), 1.28–1.20 (m, 1H), 1.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.7, 203.5, 134.4, 130.0, 129.5, 126.5, 78.0, 56.0, 53.8, 34.5, 31.0, 28.3, 26.1, 22.54, 19.1 ppm; LRMS (EI, 20 eV): *m*/*z* 304.1 (M^+, 0.5), 195.1 ($M^+-SC_6H_5$, 7), 167.1 ($M^+-COSC_6H_5$, 41); HRMS (EI, 20 eV): calcd for $C_{17}H_{20}O_3S$ (M^+), 304.1128, found 304.1125.

*4.3.6. Asymmetric reductive aldol cyclization of **6f**.* According to the general procedure in Section 4.3, Taniaphos (6.5 mg, 0.0095 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.9 mg, 0.095 mmol), and $PhSiH_3$ (48.0 μL, 0.38 mmol) in 1.5 mL PhMe was treated with **6g** (69 mg, 0.19 mmol) in PhMe (2×0.25 mL) at −10 °C for 120 h. After workup and chromatographic purification, **7f** was obtained as a white solid (49 mg, 71% yield, 96% ee) along with recovered **6g** (9.0 mg, 13% yield). Compound **7f**: $[\alpha]_D^{20}$ −112.4 (*c* 1); DAICEL CHIRALCEL AD-3, *n*-hexane/2-propanol=96/4, flow rate=0.5 mL/min, λ=254 nm, retention time: 36.4 min (minor), 43.7 min (major); R_f (25% EtOAc in hexane): 0.65; mp=100–102 °C; IR (CH_2Cl_2): 3457 (OH), 3055, 2940, 2338, 1720 (C=O, ketone), 1658 (C=O, thioester), 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.73–7.72 (m, 1H), 7.41–7.19 (m, 8H),

5.23 (s, 1H), 4.16 (d, J=13.9 Hz, 1H), 4.01 (d, J=13.9 Hz, 1H), 2.29–2.23 (m, 2H), 1.90–1.73 (m, 3H), 1.62–1.55 (m, 1H), 1.33–1.25 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 205.6, 204.8, 155.9, 136.8, 134.1, 128.7, 127.5, 123.9, 123.7, 78.7, 62.1, 56.7, 33.4, 28.5, 25.9, 24.1, 22.7; LRMS (ESI, 3 kV): m/z 389 ($M+Na^+$); HRMS (ESI, 3 kV): calcd for $C_{22}H_{22}O_3S$ ($M+Na^+$) 389.1182, found 389.1179.

4.3.7. Asymmetric reductive aldol cyclization of ***6g****.* According to the general procedure in Section 4.3, Taniaphos (5.0 mg, 0.0075 mmol), $Cu(OAc)_2\cdot H_2O$ (1.50 mg, 0.0075 mmol), and $PhSiH_3$ (38.0 μL, 0.300 mmol) in 1.0 mL PhMe was treated with **6g** (58.6 mg, 0.150 mmol) in PhMe (2×0.30 mL) at −10 °C for 120 h. After workup and chromatographic purification, **7g** was obtained as a yellow oil (32 mg, 54% yield, 95% ee), along with recovered **6g** (10.7 mg, 18% yield). Compound **7g**: $[\alpha]_D^{20}$ −137.8 (c 1); DAICEL CHIRALCEL AS-3, n-hexane/2-propanol=96/4, flow rate=1 mL/min, λ=254 nm, retention time: 9.29 min (major), 28.43 min (minor); R_f (25% EtOAc in hexane): 0.55; IR (CH_2Cl_2): 3456 (OH), 2939, 2862, 1712 (C=O, ketone), 1651 (C=O, thioester), 1604 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71–7.70 (m, 1H), 7.39–7.23 (m, 8H), 5.55 (dddd, J=23.4, 15.0, 8.4, 6.5 Hz, 1H), 5.3 (s, 1H), 4.90 (dd, J=10.1, 0.78 Hz, 1H), 4.85 (dd, J=16.9, 1.4 Hz, 1H), 4.15 (d, J=13.9 Hz, 1H), 4.00 (d, J=13.9 Hz, 1H), 2.42 (dd, J=14.2, 8.5 Hz, 1H), 2.29 (dt, J=14.2, 3.1 Hz, 1H), 2.21 (dd, J=12.3, 3.3 Hz, 1H), 1.88–1.73 (m, 3H), 1.53 (td, J=14.1, 4.5 Hz, 1H), 1.30–1.21 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.8, 203.8, 155.9, 136.7, 134.1, 133.9, 133.4, 128.8, 128.7, 128.6, 127.5, 123.7, 123.5, 117.7, 78.7, 62.5, 60.2, 41.9, 33.4, 30.9, 26.7, 25.9, 22.7 ppm; LRMS (EI, 20 eV): m/z 396.2 (M^+, 0.6), 268.1 ($M^+-SC_7H_7$, 2.59); HRMS (EI, 20 eV): calcd for $C_{24}H_{24}O_3S$ (M^+), 392.1446, found 392.1441.

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Supplementary data

The ^{1}H and ^{13}C NMR spectra of **6a**–**g** and **7a**–**g**, and chiral HPLC analyses are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.057.

References and notes

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16. The absolute stereochemistry of **7** was not determined.
17. Crystal data for (±)-**7c**. $C_{15}H_{24}O_3S$, MW=280.40, Monoclinic, space group $P\,2_1/c$, a=11.2783(3) Å, b=11.7656(3) Å, c=11.9180(3) Å, β=97.498(2)°, V=1567.95(4) Å^3, Z=4, D_x=1.205 Mg m^{-3}, μ(Mo Kα)=0.21 mm^{-1}, F(000)=616, T=296 K; crystal dimensions: 0.10×0.24×0.28 mm. All 2980 independent reflections (R_{int}=0.0403, 2231 reflections with $I>2(I)$) from a total 18,655 reflections participated in the full-matrix least-square refinement against F^2. In the final stage of least-squares refinement, all non-hydrogen atoms were refined anisotropically. Convergence $(\Delta/\sigma)_{max}<0.001$ by full-matrix least-squares refinement on F^2 reaches to R_1=0.035 and wR_2=0.097 with a goodness-of-fit of 1.030. Crystallographic data for (±)-**7c** have been deposited at the Cambridge Crystallographic Data Center, CCDC 832860.
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