

ASYMMETRIC NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES WITH OPTICALLY ACTIVE DITHIOACETALS AND THEIR APPLICATION TO OPTICALLY ACTIVE α -HYDROXY KETONE SYNTHESIS

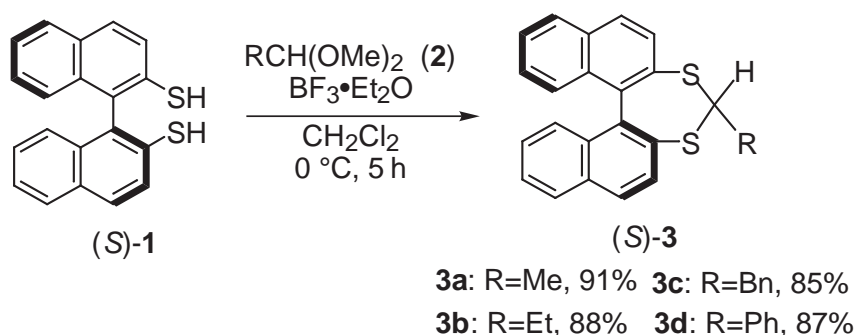
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Abstract-Optically active dithioacetals were prepared by the reaction of acetals with dithiol (**1**) having a chiral binaphthyl skeleton. Asymmetric addition reactions of various aldehydes with lithiated dithioacetals smoothly proceeded to provide the corresponding chiral alcohols (**4**) and (**5**) in fair diastereomeric excess. Moreover, preparation of optically pure α -hydroxy ketone by removal of the chiral auxiliary of **4a** was achieved without racemization.

Corey *et al.*¹ provided the first detailed study of 2-lithio-1,3-dithianes in 1965; other investigators have since utilized dithioacetals in the formation of C-C bonds.^{2,3} These compounds have seen particularly wide use for the umpolung reactions of carbonyl carbon, since the anions generated from dithioacetals are strongly stabilized by intramolecular sulfur atoms and are equivalent to acyl anions. The addition reactions of dithioacetals with aldehydes give precursors of α -hydroxy ketone derivatives, enantiomers of which are widespread in natural products and have also been used as building blocks in organic synthesis.⁴ Until recently, however, only a few attempts have been made to utilize nucleophilic addition reactions with dithioacetals in applications for stereoselective synthesis.⁵ In this paper, we report the asymmetric nucleophilic addition reactions of optically active dithioacetals with various aldehydes and their stereochemistry. Synthetic application to optically active α -hydroxy ketone by the removal of the chiral auxiliary is also described.

C_2 -Symmetrical (*S*)-dithioacetals (**3**) were synthesized in 85–91% yields by the reaction of (*S*)-**1**,⁶ which was prepared from (*S*)-1,1'-binaphthalene-2,2'-diol, with various dimethyl acetals (**2**) in the presence of boron trifluoride etherate (Scheme 1).^{5,6}



Scheme 1

Asymmetric nucleophilic addition reaction of lithiated dithioacetal ((*S*)-**3**) to benzaldehyde was carried out (Scheme 2). To a dry THF solution of (*S*)-**3a** was added *n*-butyllithium hexane solution at $-78\text{ }^{\circ}\text{C}$. After the solution was stirred for 2 h, THF solution of benzaldehyde was added dropwise to afford the corresponding optically active alcohol (**4a**) in 82% yield as a mixture of the two possible diastereoisomers. The diastereomeric excess (d.e.) of **4a**, which was determined by $^1\text{H-NMR}$ spectrum and HPLC analysis, was 80% d.e. (Table 1, Entry 1). The reaction of (*S*)-**3b** with benzaldehyde gave the corresponding chiral alcohol (**4b**) with good d.e. (88% d.e.; Entry 2). Similarly, **3c** and **3d** also proceeded to provide chiral alcohols (**4c**) and (**4d**), although these d.e.'s were not high (Entries 3 and 4).

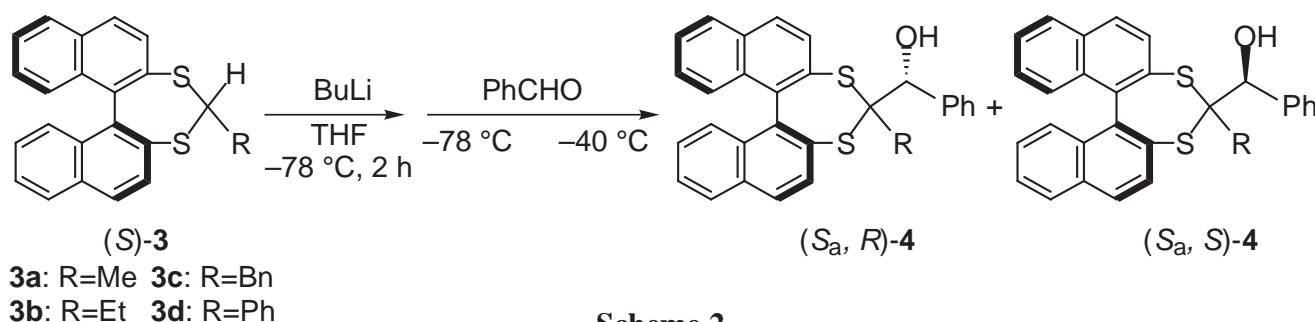


Table 1 Asymmetric nucleophilic addition reactions of benzaldehyde with 2-lithiated (*S*)-**3a–3d**

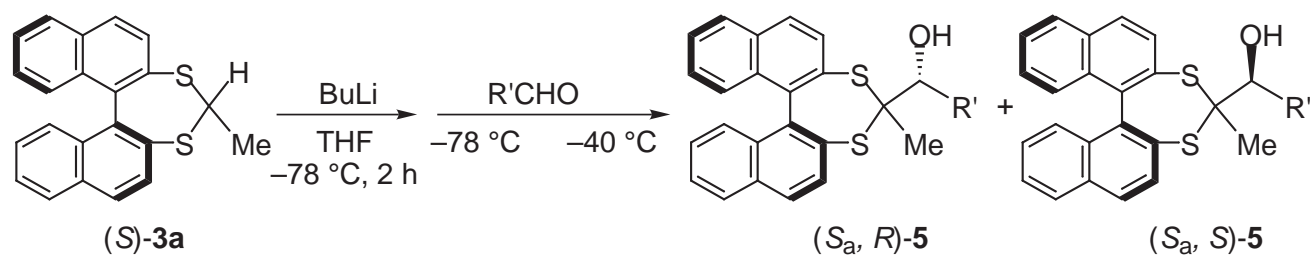
Entry	R	Product	Yield / %	D.e. / % ^a
1	Me	4a	82	80
2	Et	4b	33	88
3	Bn	4c	27	50
4	Ph	4d	21	7

^aDetermined by HPLC analysis

Next, this asymmetric nucleophilic addition reaction using optically active dithioacetal ((*S*)-**3a**) was extended to various other aldehydes under the same reaction conditions (Scheme 3). As in the case of benzaldehyde, these reactions proceeded smoothly to give the corresponding chiral alcohols (**5a–5c**) with fair d.e.'s (Table 2, Entries 2-4). This was particularly true in the case of 2-naphthaldehyde, for which chiral alcohol (**5d**) was obtained in 91% d.e. (Entry 5).

In addition, we performed separation of two obtained diastereoisomers by silica gel column chromatography. In the case of **4a**, the major isomer of the two diastereoisomers could be isolated in diastereomerically pure form.

We attempted to remove the chiral auxiliary⁷ of the obtained optically active alcohol, affording chiral α -hydroxy ketones. To the above-mentioned diastereomeric pure alcohol (**4a**) was added mercury(II)



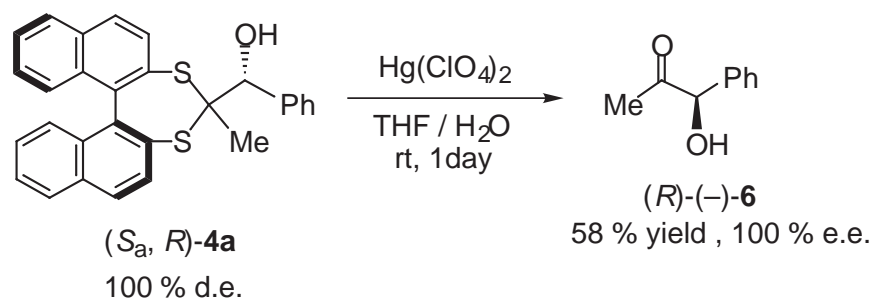
Scheme 3

Table 2 Asymmetric nucleophilic addition reactions of various aldehydes with 2-lithiated *(S)*-**3a**

Entry	R'	Product	Yield / %	D.e. / % ^a
1	Ph	4a	82	80
2		5a	67	70
3		5b	80	74
4	1-Np	5c	80	72
5	2-Np	5d	76	91

^aDetermined by HPLC analysis

perchlorate in THF and water, and the solution was stirred at rt for 1 day (Scheme 4). This deprotection reaction proceeded to provide optically pure α -hydroxy ketone (**6**) in moderate yield without racemization. The absolute configuration of **6** was found to be *R* by comparing the reported specific rotation of enantiomeric pure **6**.⁸ Consequently, the predominant absolute configuration of chiral alcohol (**4a**) was determined to be (S_a, R) .



Scheme 4

We examined MO calculations for the diastereoselectivity on the reaction of *(S)*-**3a** with benzaldehyde. Calculations were performed with the MOPAC 2000 for the MNDOd.⁹ As shown in Figure 1, there were two possible transition structures (TS 1 and TS 2) for each diastereoisomer, and these structures showed that the hydrogen atom of aldehyde located between two sulfur atoms of dithioacetal. Because of the steric hindrance between oxygen atom of benzaldehyde and methyl group of *(S)*-**3a** in TS 2, TS 1 led to

(*S*_a, *R*)-**4a** was 0.4 kcal/mol lower in energy than TS 2 led to (*S*_a, *S*)-**4a**. Consequently, these calculations were consistent with the experimental result which showed (*S*_a, *R*) selectivity in 80% d.e.

In conclusion, optically active dithioacetal ((*S*)-**3a**) can be readily prepared from the corresponding optically active dithiol ((*S*)-**1**) and acetal (**2a**). The nucleophilic addition reactions of lithiated dithioacetal ((*S*)-**3a**) with various aldehydes gave the corresponding chiral alcohols (**4**) and (**5**) with fair d.e.'s. Moreover, the conversion of (*S*_a, *R*)-**4a** into the α -hydroxy ketone ((*R*)-**6**) proceeded without racemization.

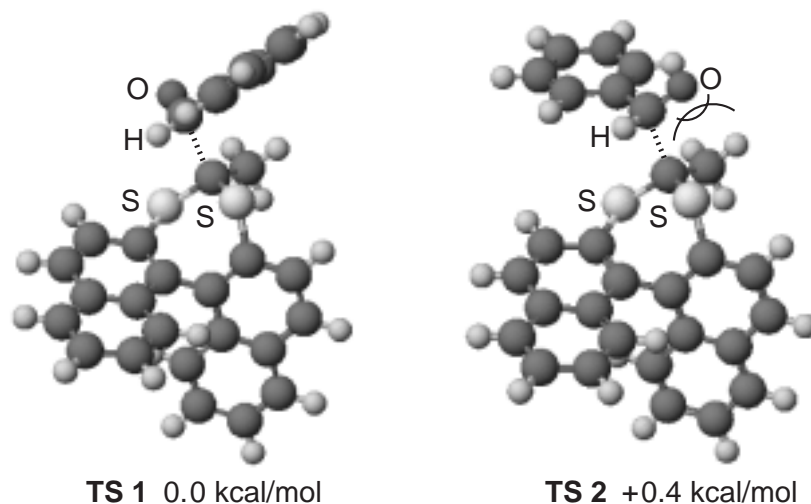


Figure 1 Modeled transition structures for the reaction of (*S*)-**3a** with benzaldehyde.

EXPERIMENTAL

General. Mps were determined with a Yamato MP-500D apparatus and uncorrected. Optical rotations were measured with JASCO DIP-1000 polarimeter. NMR spectra were recorded with a Jasco LA-500 spectrometer. HPLC analyses were performed with a Shimadzu LC-10 VP using an UV detector. THF was distilled from calcium hydride before use. Dichloromethane was distilled from calcium hydride before use. All aldehydes were freshly distilled.

(*S*)-2-Methyldinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine [(*S*)-**3a**]; General Procedure^{5,6}

To a dry dichloromethane solution (5 mL) of optically active dithiol ((*S*)-**1**) (637 mg, 2.0 mmol) and acetaldehyde dimethylacetal (360 mg, 4.0 mmol) was added dropwise boron trifluoride etherate (568 mg, 4.0 mmol) in dry dichloromethane (2 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 3 h, and slowly warmed to rt. The solution was washed with 5% potassium hydroxide aqueous solution (2×10 mL), water (2×10 mL), brine (1×10 mL) and dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and purification of the residue by silica gel chromatography (eluent: hexane/ethyl acetate=90/10) gave optically active dithioacetal ((*S*)-**3a**) (626 mg, 91%): mp 135–136 °C; [α]_D²⁷ +440.1° (c 1.36, CHCl₃); IR (KBr) 820, 1500, 3050 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.54 (3H, d, *J*=6.7 Hz), 4.93 (1H, q, *J*=6.7 Hz), 7.09–7.23 (4H, m), 7.42–7.49 (2H, m), 7.76–7.82 (2H, m), 7.90–7.98 (4H, m); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm) 23.0, 60.6, 126.28, 126.33, 126.4, 126.5, 127.4, 127.5, 128.0, 128.1, 128.2, 128.4, 128.6, 131.9, 132.0, 132.23, 132.5, 133.3, 133.78,

133.85, 142.0, 142.8; Anal. Calcd for C₂₂H₁₆S₂: C, 76.70; H, 4.68; S, 18.62. Found: C, 76.99; H, 4.91; S, 18.52.

(S)-2-Ethyldinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine [(S)-3b]: 88% yield; mp 180–181 °C; [α]_D²⁸ +330.8° (c 1.36, CHCl₃); IR (KBr) 820, 1500, 3050 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.10 (3H, t, *J*=7.1 Hz), 1.69–1.84 (2H, m), 4.71 (1H, dd, *J*=5.1, 7.1 Hz), 7.28–7.24 (4H, m), 7.42–7.48 (2H, m), 7.72–7.96 (6H, m); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm) 12.6, 29.9, 68.2, 126.28, 126.33, 126.4, 126.5, 127.6 (×2), 128.2 (×2), 128.37, 128.42, 128.7, 132.1, 132.2, 132.40, 132.44, 133.3, 133.80, 133.84, 142.2, 142.9; Anal. Calcd for C₂₃H₁₈S₂: C, 77.05; H, 5.06; S, 17.89. Found: C, 76.74; H, 5.12; S, 17.69.

(S)-2-Benzoyldinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine [(S)-3c]: 85% yield; mp 82–83 °C; [α]_D²⁸ +59.3° (c 1.30, CHCl₃); IR (KBr) 820, 1500, 3050 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 2.96 (1H, dd, *J*=5.6, 13.0 Hz), 3.12 (1H, dd, *J*=7.9, 13.0 Hz), 5.00–5.01 (1H, m), 7.08–7.51 (12H, m), 7.71–8.01 (6H, m); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm) 42.8, 67.1, 126.3, 126.40, 126.43, 126.6, 126.9, 127.5, 127.6, 128.1, 128.15, 128.19, 128.4, 128.5, 128.7, 129.4, 132.0, 132.26, 132.31, 132.4, 133.3, 133.8, 133.9, 138.2, 142.1, 143.2; HRMS found *m/z* 420.1004 (M⁺); C₂₈H₂₀S₂ requires 420.0917.

(S)-2-Phenyldinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine [(S)-3d]: 87% yield; mp 103–105 °C; [α]_D²⁸ –96.0° (c 1.37, CHCl₃); IR (KBr) 820, 1500, 3050 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 5.87 (1H, s), 7.15–7.26 (9H, m), 7.43–7.51 (2H, m), 7.64 (1H, d, *J*=8.6 Hz), 7.86 (1H, d, *J*=8.3 Hz), 7.93 (1H, d, *J*=8.3 Hz), 7.96 (2H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm) 68.4, 126.36, 126.41, 126.61, 126.64, 127.1 (×2), 127.6, 128.18, 128.19, 128.3, 128.5, 128.6, 128.7, 129.1, 131.8, 132.3, 132.4, 132.5, 133.4, 133.9, 134.0, 141.4, 142.2, 142.9; HRMS found *m/z* 406.0848 (M⁺); C₂₇H₁₈S₂ requires 406.0812.

2-Methyl-2-(1-phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (4a); General Procedure

To a dry THF solution (3 mL) of optically active dithioacetal ((*S*)-3a) (172 mg, 0.5 mmol) was added BuLi (1.6 M, 0.55 mmol) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 2 h, and benzaldehyde (80 mg, 0.75 mmol) in THF (0.5 mL) was added dropwise. The solution was slowly warmed to –40 °C over 4 h, and saturated ammonium chloride solution (5 mL) was added. After the mixture was warmed slowly to rt, the organic layer was separated. The organic component remaining in the aqueous layer was extracted with ether (3×20 mL), and the combined organic layer was dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and purification of the residue by gel-permeation chromatography (GPC) gave optically active alcohol (4a) as a mixture of the two possible diastereoisomers (184 mg, 82%). D.e. of 4a was determined by HPLC using Daicel Chiralpak AD column (hexane/ⁱPrOH=95/5): 80% d.e.; mp 112–115 °C; IR (KBr) 820, 1500, 3050, 3490 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.51 (3H×0.1, br s), 1.56 (3H×0.9, br s), 3.47 (1H×0.9, s), 3.53 (1H×0.1, s), 4.75 (1H, br s, two diastereomer), 7.08–8.04 (17H, m, two diastereomer); HRMS found *m/z* 450.1040 (M⁺); C₂₉H₂₂OS₂ requires 450.1110.

Moreover, the obtained 4a could be separated to each diastereoisomer by silica gel chromatography (eluent: hexane/ethyl acetate=90/10), and optically pure (*S*_a, *R*)-4a was isolated from first eluate.: 100% d.e., mp 123–124 °C; [α]_D³⁰ +18.8° (c 1.22, CHCl₃); IR (KBr) 820, 1500, 3050, 3480 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.55 (3H, br s), 3.48 (1H, s), 4.75 (1H, s), 7.08–8.04 (17H, m.); ¹³C NMR

(CDCl₃, 125 MHz) δ (ppm) 21.8, 77.5, 84.2, 126.5, 126.6, 126.7, 126.9, 127.6, 127.7 ($\times 2$), 127.8, 128.29, 128.32 ($\times 2$), 128.4, 128.65, 128.72, 130.9, 131.0, 132.4, 132.5, 133.2, 134.0, 134.1, 137.1, 142.7, 142.9; HRMS found m/z 450.1111 (M⁺); C₂₉H₂₂OS₂ requires 450.1175.

2-Ethyl-2-(1-phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (4b): 33% yield; 88% d.e.; mp 115-117 °C; IR (KBr) 820, 1500, 3050, 3440 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.03 (3H \times 0.94, t, $J=7.3$ Hz), 1.12 (3H \times 0.06, t, $J=7.3$ Hz), 1.77 (1H \times 0.06, qd, $J=7.3$, 14.7 Hz), 1.95 (1H \times 0.94, qd, $J=7.3$, 14.7 Hz), 2.02 (1H \times 0.06, qd, $J=7.3$, 14.7 Hz), 2.15 (1H \times 0.94, qd, $J=7.3$, 14.7 Hz), 3.57 (1H, s, two diastereomer), 4.73 (1H, s, two diastereomer), 7.06–8.03 (17H, m, two diastereomer); HRMS found m/z 464.1268 (M⁺); C₃₀H₂₄OS₂ requires 464.1268.

2-Benzyl-2-(1-phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (4c): 27% yield; 50% d.e.; mp 118-120 °C; IR (KBr) 820, 1500, 3050, 3480 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 3.21 (1H, d, $J=14.3$ Hz, two diastereomer), 3.46 (3H, s, two diastereomer), 3.52 (1H, d, $J=14.3$ Hz, two diastereomer), 4.83 (1H, s, two diastereomer), 6.98–7.95 (22H, m, two diastereomer); HRMS found m/z 526.1429 (M⁺); C₃₅H₂₆OS₂ requires 526.1423.

2-Phenyl-2-(1-phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (4d): 21% yield; 7% d.e.; mp 107-109 °C; IR (KBr) 820, 1500, 3050, 3480 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 2.85 (1H, m, two diastereomer), 4.47 (1H, s, two diastereomer), 6.65–7.98 (22H, m, two diastereomer); HRMS found m/z 465.1604 (M⁺-S); C₃₄H₂₄OS requires 465.1631.

2-Methyl-2-{1-(4'-chlorophenyl)-1-hydroxymethyl}dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (5a): 67% yield; 70% d.e.; mp 116-119 °C; IR (KBr) 820, 1490, 3450 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.46 (3H \times 0.15, br s), 1.51 (3H \times 0.85, br s), 3.51 (1H \times 0.85, s), 3.56 (1H \times 0.15, s), 4.70 (1H, br s, two diastereomer), 7.15-7.97 (16H, m, two diastereomer); HRMS found m/z 484.0727 (M⁺); C₂₉H₂₁OCIS₂ requires 484.0721.

2-Methyl-2-{1-(4'-methoxyphenyl)-1-hydroxymethyl}dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (5b): 80% yield; 74% d.e.; mp 108-111 °C; IR (KBr) 820, 1510, 3500 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.49 (3H \times 0.13, br s), 1.54 (3H \times 0.87, br s), 3.47 (1H \times 0.87, s), 3.56 (1H \times 0.13, s), 3.71 (3H \times 0.87, s), 3.75 (3H \times 0.13, s), 4.70 (1H, br s, two diastereomer), 6.78-7.97 (16H, m, two diastereomer); HRMS found m/z 481.1315 {(M+H)⁺}; C₃₀H₂₅O₂S₂ requires 481.1295.

2-Methyl-2-{1-(1'-naphthyl)-1-hydroxymethyl}dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (5c): 80% yield; 72% d.e.; mp 131-134 °C; IR (KBr) 820, 1500, 3050, 3490 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.59 (3H \times 0.14, br s), 1.65 (3H \times 0.86, br s), 3.42 (1H \times 0.86, s), 3.54 (1H \times 0.14, s), 5.77 (1H, br s, two diastereomer), 7.05-8.04 (19H, m, two diastereomer); HRMS found m/z 500.1306 (M⁺); C₃₃H₂₄OS₂ requires 500.1267.

2-Methyl-2-{1-(2'-naphthyl)-1-hydroxymethyl}dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepine (5d): 76% yield; 91% d.e.; mp 138-140 °C; IR (KBr) 820, 1500, 3050, 3480 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 1.60 (3H, br s, two diastereomer), 3.62 (1H \times 0.955, s), 3.65 (1H \times 0.045, s), 4.91 (1H, br s, two diastereomer), 7.11-8.04 (19H, m, two diastereomer); HRMS found m/z 500.1245 (M⁺); C₃₃H₂₄OS₂ requires 500.1267.

Preparation of the chiral α -hydroxy ketone: (*R*)-1-hydroxy-1-phenyl-2-propanone [(*R*)-6]

A solution of optically pure (S_a , R)-**4a** (159 mg, 0.33 mmol) in THF (2.5 mL) and water (0.5 mL) was stirred at rt in the presence of calcium carbonate (400 mg), and mercury(II) perchlorate aqueous solution (4 M, 0.1 mL) was added dropwise in 5 min. After the solution was stirred an additional 1 day, ether (20 mL) was added and the mixture filtered. The filtrate was extracted with ether (3×10 mL), and the organic layer was dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and purification of the residue by GPC gave optically pure α -hydroxy ketone (**6**) (29 mg, 58%): 100% e.e.; $[\alpha]_D^{25} +161.3^\circ$ (c 0.8, EtOH) lit.,⁸ $[\alpha]_D +164.7^\circ$ (c 2.2, EtOH).

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