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Synthesis of new chiral thiazoline-containing ligands

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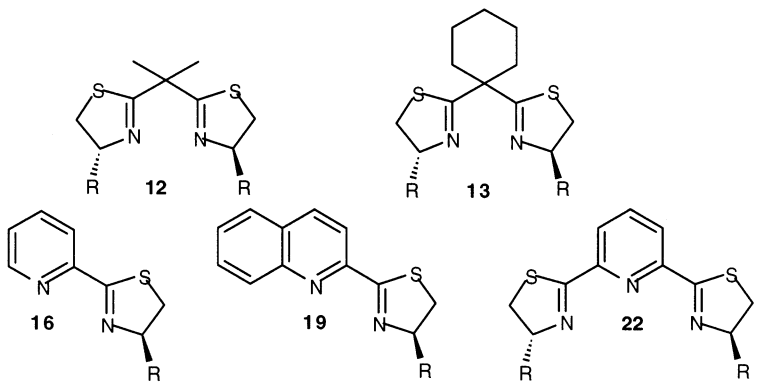
Abstract—New chiral ligands, including bi- and tridentate thiazoline derivatives, analogues of known oxazolines, have been synthesized by a general and convenient procedure, starting from dithioesters and commercial enantiopure 2-aminoalcohols. A preliminary test shows the ability of such ligands to act as asymmetric catalysts in Pd-catalyzed allylic substitution reaction.

1. Introduction

Chiral oxazolines and bis-oxazolines are well known ligands for metals, used as efficient asymmetric catalysts in various reactions.[1] Several of their sulfur analogues are known, but the variety of structures is very restricted as far as chiral bis-thiazolines are concerned.[2,3] This is probably because the most usual sulfur-containing precursors, the 2-aminothiols, are not easily available (compared to the corresponding aminoalcohols). Electronic and steric effects, resulting from the substitution of the oxygen by the sulfur, could change the behavior of the chelating heterocycle towards metals. Thus, the exploration of thiazolines as ligands in asymmetric catalysis and their comparison with oxazolines represents an attractive study. Furthermore, to the best of our knowledge, only two examples of thiazoline metal complexes have been used for this purpose: Rh(I) complexes in hydrosilylation[2] and Cu(II) complexes in cyclopropanation.[3] We recently described a facile access to chiral phosphonylated thiazolines (used as new Horner–Wadsworth–Emmons reagents) starting from ethyl phosphonodithioacetate and enantiopure 2-aminoalcohols.[4] We have now extended and adapted this procedure, by using dithioesters, easily accessible in a wide variety of structures, as sulfur sources replacing aminothiols. This method allowed us to prepare new ligands, including alkylidene bis(thiazolines), 2-pyridyl and 2-quinolyl thiazolines and 2,6-pyridyl bis(thiazolines), analogous of the well known corresponding oxazolines (Scheme 1). A first estimation of the ability of these new ligands to act in asymmetric Pd-catalyzed reactions has also been demonstrated by using one of them in allylic substitution.



Scheme 1.

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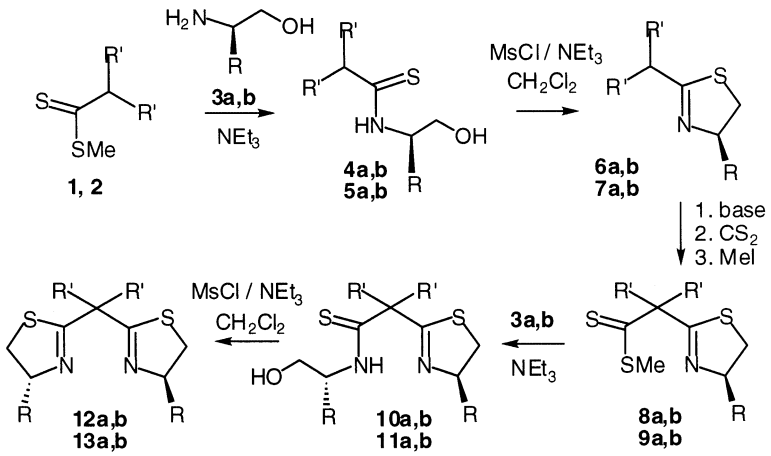


Scheme 2.

Table 1.

Starting dithioester	Aminoalcohol	R	R′,R′	Product	Overall yield of **12** and **13** (%)
1	**3a**	Et	Me,Me	**12a**	78
1	**3b**	*i*Pr	Me,Me	**12b**	76
2	**3a**	Et	$(CH_2)_5$	**13a**	75
2	**3b**	*i*Pr	$(CH_2)_5$	**13b**	73

2. Results and discussion

2.1. Synthesis of bidentate bis(thiazolines) 12 and 13

The general synthetic route is summarized in Scheme 2. The thioamides **4a**,**b** and **5a**,**b** were readily prepared in nearly quantitative yield by thioacylation of the commercially available aminoalcohols **3a**,**b** with the appropriate starting dithioesters **1** or **2**. The intramolecular cyclization via an *S*-alkylation, using mesyl chloride and triethylamine in dichloromethane, led to alkyl thiazolines **6a**,**b** and **7a**,**b**. The yield of isolated thiazolines (95–99%) was much improved by this method, in comparison to the Mitsunobu procedure, previously used in phosphonate series[4] (due to the formation of Ph_3PO, purification is more difficult). The intermediate thiazoline-dithioesters **8a**,**b** and **9a**,**b** were obtained by α-metallation of thiazolines **6** or **7**, using *t*-BuLi, followed by the condensation of the carbanion with carbon disulfide and *S*-alkylation with methyl iodide (yield = 79–85%).[5] From **8** or **9** the same subsequent two-step process (amination with **3a**,**b** and cyclization of **10** and **11**) led to bis(thiazolines) **12** and **13**. Based on **1** or **2**, the overall yields of **12a**,**b** and **13a**,**b** are given in Table 1.

2.2. Synthesis of 2-pyridyl thiazolines 16, 2-quinolyl thiazolines 19 and 2,6-pyridyl bis-thiazolines 22

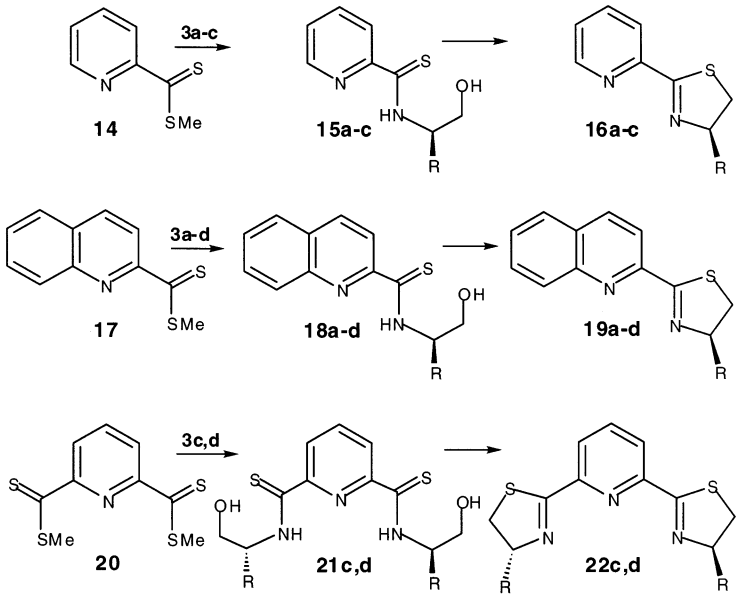
Starting from the corresponding dithioesters **14**, **17** and **20**, prepared respectively from 2-picolyl chloride,[6,7] 2-chloromethyl quinoline[6] and 2,6-di(chloromethyl) pyridine,[8] and using the same procedure (involving the generation of intermediate thioamides **15**, **18** and **21** and in situ intramolecular cyclization of their mesylates), we were able to prepare respectively functionalized thiazolines **16** and **19** and bis-thiazoline **22**, potential bidentate and tridentate ligands (Scheme 3). Based on starting dithioester, the overall yields are given in Table 2.

2.3. Preliminary test of new ligand 12a in a Pd-catalyzed allylic substitution

Palladium-catalyzed asymmetric allylic substitution, especially the alkylation of 1,3-diphenyl-2-propenyl acetate with malonate (Scheme 4), is a significant C–C bond-forming reaction in organic synthesis.[9] This model reaction was carried out as a preliminary test on the possibility of using these type of thiazoline ligand in an asymmetric catalyst. With the first tested bis(thiazoline) **12a**, we obtained a very good yield (90%) and high enantiomeric excess (87%). The comparison of our HPLC data with that described in the literature[10] allowed us to assign the absolute configuration *S* to the major enantiomer of the (*E*)-methyl 2-methoxycarbonyl-3,5-diphenylpent-4-enoate. A systematic study on the efficiency of all the new prepared ligands in this allylation reaction will be undertaken and published in due course.

3. Conclusion

In summary, we have developed a convenient and general route to various new chiral bi- and tridentate ligands based on the thiazoline ring, starting from dithioesters and commercial enantiopure 2-aminoalcohols. The high enantiomeric excess (87%) observed in a Pd-catalyzed allylic substitution using one of the syn-



Scheme 3.

thesized bis(thiazolines), indicates that these ligands are promising in asymmetric catalysis using this transition metal. Further studies concerning their complexing properties towards various metal cations and applications in other type of metal-catalyzed reactions will be undertaken in order to determine their specificity compared to that of bis-oxazolines.

4. Experimental

4.1. General

Most of reactions were carried out under a nitrogen atmosphere with magnetic stirring, unless otherwise specified and monitored by TLC using silica plates. Synthesized products were purified by flash column chromatography on silica gel or recrystallised if necessary. Solvents were dried by distillation prior use. The NMR spectra were recorded in $CDCl_3$, with a 'Bruker AC 250' or a 'Bruker AC 400' spectrometer. The chemical shifts (δ) are expressed in ppm relative to TMS for H and C nuclei, the coupling constants (J) are given in Hz; conventional abbreviations are used. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter for the sodium D line at 20°C. Melting points are uncorrected. The infrared spectra were recorded with a Perkin–Elmer 16 PC spectrometer on the liquid film, ν (cm^{-1}) are given. Mass spectra were recorded with a Nermag R 10 10H spectrometer in electronic-impact mode at 70 eV, m/z and relative abundance are given. HRMS were obtained with a JEOL JMS-AX 500 mass spectrometer. Elemental microanalyses were performed at Caen with an automatic apparatus CHNS-O ThermoQuest. Microanalyses or HRMS and specific rotation are given only for the final compounds (thiazolines **12a**,**b**, **13a**,**b**, **16a**–**c**, **19a**–**d**, **22c**,**d**). The abbreviations used for the solvents are: P = pentane, DEE = diethylether).

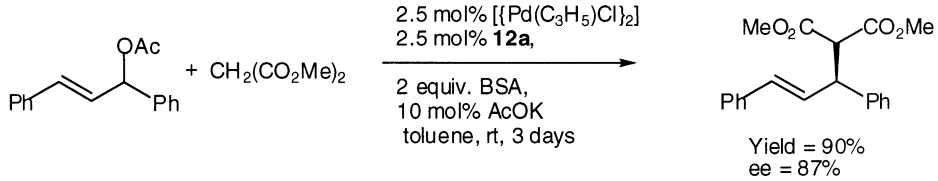
4.2. General procedure A for the preparation of thioamides 4, 5, 10, 11, 15, 18 and 21[†]

A mixture of dithioester (**1**, **2**, **8**, **9**, **14** or **17**, 15 mmol), aminoalcohol (the commercial aminoalcohols used in the reaction were (*R*)-(−)-2-aminobutanol, (*R*)-(−)-valinol, (*R*)-(−)-phenylglycinol and (*S*)-(+)-*tert*-leucinol) **3** (15 mmol) and triethylamine (19 mmol) was stirred at room temperature (for the dithioesters **14**, **17** and **20**, 1 mL THF/mmol dithioester was used as solvent). The end of the reaction was controlled by TLC (time: 2 h to 4 days). Then, the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the thioamide.

Table 2.

Starting dithioester	Aminoalcohol	R	Product	Overall yield (%)
14	**3a**	Et	**16a**	91
14	**3b**	*i*Pr	**16b**	90
14	**3c**	Ph	**16c**	90
17	**3a**	Et	**19a**	90
17	**3b**	*i*Pr	**19b**	87
17	**3c**	Ph	**19c**	85
17	**3d**	*t*Bu	**19d**	82
20	**3c**	Ph	**22c**	56
20	**3d**	*t*Bu	**22d**	55

[†] For the bis-thioamides **21**, the corresponding stoichiometry was used: bis-dithioester **20** (15 mmol) aminoalcohol **3** (30 mmol) and NEt_3 (38 mmol) in 15 mL of THF.



Scheme 4.

4.2.1. (*R*)-*N*-[1-(Hydroxymethyl)propyl]-2-methylpropanethioamide 4a. Prepared according to the general procedure **A** starting from dithioester **1** and aminoalcohol **3a** (time: 12 h); yellow oil, yield = 98%, R_f = 0.4 (P/DEE: 30/70); ^{1}H NMR: δ 0.98 (t, J = 7.5, 3H, C**H**$_3$CH$_2$), 1.26 (d, J = 6.8, 6H, HC(C**H**$_3$)$_2$), 1.64–1.78 (m, 2H, CH$_3$C**H**$_2$), 2.76 (br s, 1H, O**H**), 2.81 (sept., J = 6.8, 1H, **H**C(CH$_3$)$_2$), 3.79 (dd, J_1 = 11.1, J_2 = 3.7, 1H, C**H**HO), 3.83 (dd, J_1 = 11.1, J_2 = 4.5, 1H, CH**H**O), 4.63 (m, 1H, C**H**N), 7.3 (br s, 1H, N**H**); ^{13}C NMR: δ 10.8 (CH$_2$**C**H$_3$), 22.9 and 23.0 (CH(**C**H$_3$)$_2$), 23.7 (**C**H$_2$CH$_3$), 45.0 (**C**H(CH$_3$)$_2$), 58.0 (**C**HNH), 63.5 (**C**H$_2$OH), 212.2 (**C**=S).

4.2.2. (*R*)-*N*-[1-(Hydroxymethyl)-2-methylpropyl]-2-methylpropanethioamide 4b. Prepared according to the general procedure **A** starting from dithioester **1** and aminoalcohol **3b** (time: 12 h); yellow oil, yield = 98%, R_f = 0.42 (P/DEE: 30/70); ^{1}H NMR: δ 0.98 (d, J = 6.9, 6H, HC(C**H**$_3$)$_2$), 1.28 (d, J = 6.8, 6H, C(*S*)HC(C**H**$_3$)$_2$), 2.06 (m, 1H, **H**C(CH$_3$)$_2$), 2.49 (br s, 1H, O**H**), 2.81 (sept., J = 6.8, 1H, C(*S*)**H**C(CH$_3$)$_2$), 3.78 (dd, J_1 = 11.2, J_2 = 3.8, 1H, C**H**HO), 3.85 (dd, J_1 = 11.2, J_2 = 4.8, 1H, CH**H**O), 4.58 (m, 1H, C**H**N), 7.56 (br s, 1H, N**H**); ^{13}C NMR: δ 19.4 and 19.7 (HC(**C**H$_3$)$_2$), 22.9 and 23.0 (HC(**C**H$_3$)$_2$), 29.3 (H**C**(CH$_3$)$_2$), 45.4 (**C**(CH$_3$)$_2$), 61.7 (**C**HN), 62.7 (**C**H$_2$O), 212.5 (**C**=S); IR (NaCl): 3260 (ν_{OH}), 3050 (ν_{NH}), 2960, 2870, 1520 ($\nu_{N-C=S}$), 1430, 1070, 1010.

4.2.3. (*R*)-*N*-[1-(Hydroxymethyl)propyl]cyclohexanethiocarboxamide 5a. Prepared according to the general procedure **A** starting from dithioester **2** and aminoalcohol **3a** (time: 2 days); yellow oil, yield = 98%, R_f = 0.24 (P/DEE: 50/50); ^{1}H NMR: δ 0.91 (t, J = 7.5, 3H, C**H**$_3$CH$_2$), 1.1–1.8 (m, 12H, CH$_3$C**H**$_2$ and (C**H**$_2$)$_5$), 2.35 (m, 1H, O**H**), 3.72 (dd, J_1 = 11.1, J_2 = 3.7, 1H, C**H**HO), 3.83 (dd, J_1 = 11.1, J_2 = 4.5, 1H, CH**H**O), 4.63 (m, 1H, C**H**N), 7.45 (br s, 1H, N**H**); ^{13}C NMR: δ 10.8 (**C**H$_3$CH$_2$), 23.7 (CH$_3$**C**H$_2$), 25.9, 26.2, 26.3, 33.1, 33.2, 55.5, 57.9 (**C**HN), 63.5 (**C**H$_2$O), 210.9 (N**C**=S); IR (NaCl): 3600, 3450 (ν_{OH}), 3320 (ν_{NH}), 2980, 2850, 1550 ($\nu_{N-C=S}$), 1440, 1370.

4.2.4. (*R*)-*N*-[1-(Hydroxymethyl)-2-methylpropyl]cyclohexanethiocarboxamide 5b. Prepared according to the general procedure **A** starting from dithioester **2** and aminoalcohol **3b** (time: 2 days); white solid, mp = 90°C, yield = 98%, R_f = 0.36 (P/DEE: 50/50); ^{1}H NMR: δ 0.99 and 1.01 (2d, J = 6.7, 6H, CH(C**H**$_3$)$_2$), 1.31–2.01 (m, 10H, (C**H**$_2$)$_5$), 2.54 (m, 1H, C**H**(CH$_3$)$_2$), 2.74 (br s, 1H, O**H**), 2.85 (sept., J = 6.8, 1H, C**H**(CH$_3$)$_2$), 3.75 (dd, J_1 = 11.2, J_2 = 3.8, 1H, C**H**HO), 3.87 (dd, J_1 = 11.2, J_2 = 4.7, 1H, CH**H**O), 4.60 (m, 1H, C**H**NH), 7.27 (br s, 1H, N**H**); ^{13}C NMR: δ 19.5 and 19.7 (CH(**C**H$_3$)$_2$), 26.0, 26.3, 26.4, 29.4 (**C**H(CH$_3$)$_2$), 33.2, 33.3, 61.5 (**C**HNH), 63.0 (**C**H$_2$OH), 211.3 (**C**=S); IR (NaCl): 3205 (ν_{OH}), 3060 (ν_{NH}), 2920, 2852, 1654, 1564, 1450, 1350, 1056.

4.2.5. (*R*,*R*)-4-Ethyl-2-{1-[*N*-(1-(hydroxymethyl)propyl)-thiocarbamoyl]-1-methylethyl}-2-thiazoline 10a. Prepared according to the general procedure **A** starting from dithioester **8a** and aminoalcohol **3a** (24 h); yellow oil, yield = 98%, R_f = 0.55 (P/DEE: 50/50); ^{1}H NMR: δ 0.93 (t, J = 7.4, 6H, C**H**$_3$CH$_2$), 1.04 (t, J = 7.4, 6H, C**H**$_3$CH$_2$), 1.53–1.85 (m, 4H, 2×CH$_3$C**H**$_2$), 1.65 and 1.66 (2s, 6H, C(C**H**$_3$)$_2$), 2.6 (br s, 1H, O**H**), 3.04 (dd, J_1 = 11.0, J_2 = 8.6, 1H, C**H**HS), 3.28 (dd, J_1 = 11.0, J_2 = 8.4, 1H, CH**H**S), 3.71 (dd, J_1 = 11.2, J_2 = 3.9, 1H, C**H**HO), 3.90 (dd, J_1 = 11.2, J_2 = 4.3, 1H, CH**H**O), 4.10 (m, 1H, C**H**N), 9.35 (br s, 1H, N**H**); ^{13}C NMR: δ 10.8 (CH$_2$**C**H$_3$), 11.0 (CH$_2$**C**H$_3$), 23.7 (**C**H$_2$CH$_3$), 28.3 (**C**H$_2$CH$_3$), 29.8 and 30.3 (C(**C**H$_3$)$_2$), 37.6 (**C**H$_2$S), 53.0 (**C**(CH$_3$)$_2$), 59.0 (**C**HNH), 63.6 (**C**H$_2$OH), 79.1 (**C**HN), 177.8 (S–**C**=N), 205.9 (**C**=S).

4.2.6. (*R*,*R*)-4-Isopropyl-2-{1-*N*-[(1-hydroxymethyl)-2-methylpropyl)thiocarbamoyl]-1-methylethyl}-2-thiazoline 10b. Prepared according to the general procedure **A** starting from dithioester **8b** and aminoalcohol **3b** (time: 2 days); yellow oil, yield = 98%, R_f = 0.6 (P/DEE: 50/50); ^{1}H NMR: δ 0.97 and 1.03 and 1.08 (3d, J = 6.8, 12H, 4×C**H**$_3$), 1.67 and 1.71 (2s, 6H, C(C**H**$_3$)$_2$), 2.04 (sept., J = 6.8, 2H, 2×C**H**(CH$_3$)$_2$), 2.6 (br s, 1H, O**H**), 2.98 (dd, J_1 = 11.4, J_2 = 8.9, 1H, C**H**HS), 3.27 (dd, J_1 = 11.4, J_2 = 10.1, 1H, CH**H**S), 3.72 (dd, J_1 = 11.2, J_2 = 3.6, 1H, C**H**HO), 3.88 (dd, J_1 = 11.2, J_2 = 5.3, 1H, CH**H**O), 4.28 (dt, J_1 = 8.9, J_2 = 6.5, 1H, C**H**N=C), 4.56 (m, 1H, C**H**NH), 9.75 (br s, 1H, N**H**); ^{13}C NMR: δ 19.3, 19.4, 19.8, 20.0, 29.4, 30.0, 30.8, 33.4, 35.3 (**C**H$_2$S), 53.17 (C(CH$_3$)$_2$), 63.0 (**C**HNH), 63.1 (CH$_2$O), 83.9 (**C**HN), 178.0 (S**C**=N), 206.5 (NH**C**=S); IR (NaCl): 3400 (ν_{OH}), 3350 (ν_{NH}), 2930, 2870, 1600, 1520 ($\nu_{N-C=S}$), 1460, 1040.

4.2.7. (*R*,*R*)-4-Ethyl-2-{1-[*N*-(1-(hydroxymethyl)propyl)-thiocarbamoyl]cyclohexyl}-2-thiazoline 11a. Prepared according to the general procedure **A** starting from dithioester **9a** and aminoalcohol **3a** (time: 4 days); yellow solid, mp = 86°C, yield = 98%, R_f = 0.69 (P/DEE: 20/80); ^{1}H NMR: δ 0.97 (t, J = 7.4, 3H, C**H**$_3$CH$_2$), 1.05 (t, J = 7.4, 3H, C**H**$_3$CH$_2$), 1.56–2.17 (m, 15H, 2× CH$_3$C**H**$_2$ and (C**H**$_2$)$_5$ and O**H**), 2.97 (dd, J_1 = 10.9, J_2 = 7.7, 1H, C**H**HS), 3.37 (dd, J_1 = 10.9, J_2 = 8.6, 1H, CH**H**S), 3.64 (dd, J_1 = 11.2, J_2 = 4.0, 1H, C**H**HO),

3.87 (dd, $J_1=11.2$, $J_2=3.5$, 1H, CH**H**O), 4.62 (m, 1H, C**H**NH), 4.48 (m, 1H, C**H**N=C), 8.05 (br s, 1H, N**H**); ^{13}C NMR: δ 10.8 (**C**H_3CH$_2$), 11.3 (**C**H_3CH$_2$), 23.3, 23.4, 23.7, 25.4, 28.1, 37.0, 37.2, 37.6 (**C**H_2S), 58.0, 58.4 (**C**HNH), 63.2 (CH$_2$OH), 78.9 (**C**HN), 175.6 (NH**C**=S), 205.3 (S**C**=N); IR (KBr): 3340 (ν_{OH}), 3260 (ν_{NH}), 2960, 2850, 1600 ($\nu_{S-C=N}$), 1502 ($\nu_{N-C=S}$), 1450, 1195, 1018.

4.2.8. (*R*,*R*)-4-Isopropyl-2-{1-[*N*-(1-(hydroxymethyl)-2-methylpropyl)thiocarbamoyl]cyclohexyl}-2-thiazoline 11b. Prepared according to the general procedure **A** starting from dithioester **9b** and aminoalcohol **3b** (4 days); yellow solid, yield = 98%, $R_f=0.92$ (P/DEE: 20/80); ^{1}H NMR: δ 0.97 and 1.01 and 1.09 (3d, $J=7.8$, 12H, 2×CH(C**H**$_3$)$_2$), 1.02–2.45 (m, 13H, O**H**, (C**H**$_2$)$_5$, 2×C**H**(CH$_3$)$_2$), 3.01 (dd, $J_1=10.9$, $J_2=9.9$, 1H, C**H**HS), 3.28 (dd, $J_1=10.9$, $J_2=8.9$, 1H, CH**H**S), 3.69–3.84 (m, 2H, C**H**$_2$O), 4.26 (m, 1H, C**H**N=C), 4.51 (m, 1H, C**H**NH), 8.15 (br s, 1H, N**H**); ^{13}C NMR: δ 19.3, 19.8, 20.2, 23.3, 23.6, 25.4, 29.3, 33.3, 35.4, 36.9, 37.3 (**C**H$_2$S), 58.3, 62.4 (**C**HNH), 66.2 (CH$_2$O), 83.9 (**C**HN), 175.5 (S**C**=N), 205.6 (NH**C**=S); IR (NaCl): 3500 (ν_{OH}), 3330 (ν_{NH}), 2930, 2870, 1600 ($\nu_{S-C=N}$), 1520 ($\nu_{N-C=S}$), 1460, 1390, 1228, 1070.

4.2.9. (*R*)-*N*-[1-(Hydroxymethyl)propyl]-2-pyridinethiocarboxamide 15a. Prepared according to the general procedure **A** starting from dithioester **14** and aminoalcohol **3a** (time: 2 h); yellow oil, yield = 93%, $R_f=0.34$ (P/DEE: 50/50); ^{1}H NMR: δ 0.94 (t, $J=7$, 3H, C**H**$_3$CH$_2$), 1.75 (m, 2H, C**H**$_2$CH$_3$), 2.58 (br s, 1H, O**H**), 3.76 (dd, $J_1=11.2$, $J_2=4.8$, 1H, C**H**HO), 3.86 (dd, $J_1=11.2$, $J_2=3.9$, 1H, CH**H**O), 4.35 (m, 1H, C**H**N), 7.33 (ddd, $J_1=4.7$, $J_2=7.5$, $J_3=1.1$, 1H, CH^{Py}), 7.74 (dt, $J_1=7.5$, $J_2=1.8$, $J_3=7.5$, 1H, CH^{Py}), 8.41 (d, $J=4$, 1H, CH^{Py}), 8.6 (d, $J=8$, 1H, CH^{Py}), 10.20 (br s, 1H, NH); ^{13}C NMR: δ 10.78 (CH$_2$**C**H$_3$), 23.78 (**C**H$_2$CH$_3$), 58.4 (**C**HN), 60.6 (**C**H$_2$O), 125.4, 126.4, 137.6, 147.3, 151.6, 191.4 (N**C**=S); IR (NaCl): 3380 and 3460 (ν_{OH}), 3260 (ν_{NH}), 2950, 1505 ($\nu_{N-C=S}$), 1455, 1430, 1370, 1330.

4.2.10. (*R*)-*N*-[1-(Hydroxymethyl)-2-methylpropyl]-2-pyridinethiocarboxamide 15b. Prepared according to the general procedure **A** starting from dithioester **14** and aminoalcohol **3b** (time: 2 h). yellow oil, yield = 92%, $R_f=0.61$ (P/DEE: 40/60); ^{1}H NMR: δ 1.04 and 1.07 (2d, $J=6.7$, 6H, CH(C**H**$_3$)$_2$), 2.20 (m, 1H, C**H**(CH$_3$)$_2$), 2.55 (s, 1H, O**H**), 3.91–4.15 (m, 2H, C**H**$_2$O), 4.70 (m, 1H, C**H**N), 7.41 (m, 1H, CH^{Py}), 7.82 (m, 1H, CH^{Py}), 8.49 (m, 1H, CH^{Py}), 8.68 (dd, $J_1=8.0$, $J_2=1.0$, 1H, CH^{Py}), 10.25 (br s, 1H, NH); ^{13}C NMR: δ 19.3 and 19.8 (CH(**C**H$_3$)$_2$), 29.5 (**C**H(CH$_3$)$_2$), 62.4 (CHN), 63.0 (CH$_2$O), 125.5, 126.3, 137.5, 147.3, 151.4, 191.6 (N**C**=S); IR (NaCl): 3280 (ν_{OH}), 3050 (ν_{NH}), 2960, 2880, 1580 ($\nu_{N-C=S}$), 1460, 1340.

4.2.11. (*R*)-*N*-[2-Hydroxy-1-phenylethyl]-2-pyridinethiocarboxamide 15c. Prepared according to the general procedure **A** starting from dithioester **14** and aminoalcohol **3c** (time: 4 h); yellow solid, mp = 132°C, yield = 95%, $R_f=0.46$ (P/DEE: 30/70); ^{1}H NMR: δ 2.05 (s, 1H, O**H**), 4.15 (m, 2H, C**H**$_2$O), 5.92 (m, 1H, C**H**N), 7.27–7.46 (m, 6H, CH^{Py} and C$_6$H$_5$), 7.83 (dt, $J_1=7.7$, $J_2=1.7$, $J_3=7.7$, 1H, CH^{Py}), 8.52 (d, $J=4.5$, 1H, CH^{Py}), 8.68 (d, $J=8$, 1H, CH^{Py}), 10.95 (br s, 1H, NH); ^{13}C NMR: δ 60.6 (**C**HN), 66.1 (**C**H$_2$O), 125.4, 126.5, 127.4, 128.4, 129.4, 137.7, 138.5, 147.4, 151.5, 191.4 (N**C**=S); IR (KBr): 3648 (ν_{OH}), 3255 (ν_{NH}), 2940, 2792, 1624 ($\nu_{N-C=S}$).

4.2.12. (*R*)-*N*-[1-(Hydroxymethyl)propyl]-2-quinolinethiocarboxamide 18a. Prepared according to the general procedure **A** starting from dithioester **17** and aminoalcohol **3a** (time: 24 h); yellow oil, yield = 95%, $R_f=0.54$ (P/DEE: 30/70); ^{1}H NMR: δ 1.07 (t, $J=7.5$, 3H, C**H**$_3$CH$_2$), 1.9 (q, $J=7.5$, 2H, CH$_3$C**H**$_2$), 2.24 (s, 1H, O**H**), 3.85 (dd, $J_1=11.2$, $J_2=4.8$, 1H, C**H**HO), 3.95 (dd, $J_1=11.2$, $J_2=3.8$, 1H, CH**H**O), 4.81 (m, 1H, C**H**N), 7.59 (ddd, $J_1=8.2$, $J_2=6.9$, $J_3=1.4$, 1H, CH^{Qi}), 7.76 (ddd, $J_1=8.4$, $J_2=6.9$, $J_3=1.1$, 1H, CH^{Qi}), 7.85 (d, $J=8.2$, 1H, CH^{Qi}), 8.11 (d, $J=8.4$, 1H, CH^{Qi}), 8.26 (d, $J=8.6$, 1H, CH^{Qi}), 8.83 (d, $J=8.65$, 1H, CH^{Qi}), 10.45 (br s, 1H, NH); ^{13}C NMR: δ 14.2 (**C**H$_3$CH$_2$), 24.2 (CH$_3$**C**H$_2$), 58.9 (**C**HN), 64.4 (**C**H$_2$O), 122.1, 128.2, 122.6, 130.4, 130.8, 137.5, 145.6, 150.6, 174.8 (N**C**=S); IR (NaCl): 3380 (ν_{OH}), 3280 (ν_{NH}), 2960, 2900, 1500 ($\nu_{N-C=S}$).

4.2.13. (*R*)-*N*-[1-(Hydroxymethyl)-2-methylpropyl]-2-quinolinethiocarboxamide 18b. Prepared according to the general procedure **A** starting from dithioester **17** and aminoalcohol **3b** (time: 24 h); orange oil, yield = 92%, $R_f=0.6$ (P/DEE: 30/70); ^{1}H NMR: δ 1.13 and 1.14 (2d, $J=6.8$, 6H, CH(C**H**$_3$)$_2$), 2.1 (s, 1H, O**H**), 2.31 (m, 1H, C**H**(CH$_3$)$_2$), 3.97 (dd, $J_1=11.4$, $J_2=5.5$, 1H, C**H**HO), 4.05 (dd, $J_1=11.4$, $J_2=3.8$, 1H, CH**H**O), 4.77 (m, 1H, C**H**N), 7.63 (ddd, $J_1=8.1$, $J_2=7.6$, $J_3=1.0$, 1H, CH^{Qi} **H**$_9$), 7.78 (ddd, $J_1=8.4$, $J_2=7$, $J_3=1.4$, 1H, CH^{Qi}), 7.88 (d, $J=8.1$, 1H, CH^{Qi}), 8.13 (d, $J=8.4$, 1H, CH^{Qi}), 8.29 (d, $J=8.6$, 1H, CH^{Qi}), 8.85 (d, $J=8.6$, 1H, CH^{Qi}), 10.62 (br s, 1H, NH); ^{13}C NMR: δ 19.4 and 20.0 (CH(**C**H$_3$)$_2$), 29.7 (**C**H(CH$_3$)$_2$), 62.6 (**C**HN), 63.4 (**C**H$_2$O), 122.1, 128.0, 128.4, 129.6, 130.4, 130.7, 137.4, 145.8, 150.6, 192.1 (N**C**=S); IR (NaCl): 3280 (ν_{OH}), 3060 (ν_{NH}), 2960, 2870, 1590 ($\nu_{N-C=S}$), 1500, 1380.

4.2.14. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2-quinolinethiocarboxamide 18c. Prepared according to the general procedure **A** starting from dithioester **17** and aminoalcohol **3c** (time: 24 h); orange oil, yield = 90%, $R_f=0.50$ (P/DEE: 50/50); ^{1}H NMR: δ 2.1 (s, 1H, O**H**), 4.20 (d, $J=4.5$, 2H, C**H**$_2$O), 5.96 (dt, $J_1=7.0$, $J_2=4.5$, 1H, C**H**N), 7.61 (ddd, $J_1=8.1$, $J_2=6.9$, $J_3=1.1$, 1H, CH^{Qi}), 7.28–7.47 (m, 5H, C$_6$H$_5$), 7.76 (ddd, $J_1=8.4$, $J_2=6$, $J_3=1.5$, 1H, CH^{Qi}), 7.86 (d, $J=8.1$, 1H, CH^{Qi}), 8.15 (d, $J=8.4$, 1H, CH^{Qi}), 8.25 (d, $J=8.6$, 1H, CH^{Qi}), 8.81 (d, $J=8.65$, 1H, CH^{Qi}), 11.02 (d, $J=7.0$, 1H, NH); ^{13}C NMR: δ 60.82 (**C**HN), 66.0 (**C**H$_2$O), 121.9, 127.0, 127.4, 128.0, 128.4, 128.4, 129.3, 129.6, 130.4, 137.3, 138.1, 145.8, 150.5, 191.4 (N**C**=S); IR (KBr): 3400 (ν_{OH}), 3280 (ν_{NH}), 2960, 2900, 1590 ($\nu_{N-C=S}$), 1490, 1370.

4.2.15. (*S*)-*N*-[1-(Hydroxymethyl)-2,2-dimethylpropyl]-2-quinolinethiocarboxamide 18d. Prepared according to the general procedure **A** starting from dithioester **17** and aminoalcohol **3d** (time: 24 h); orange oil, yield =

87%, R_f=0.6 (P/DEE: 50/50). ^{1}H NMR: 1.17 (s, 9H, C(C**H**$_3$)$_3$), 2.2 (s, 1H, O**H**), 3.92–4.18 (m, 2H, C**H**$_2$O), 4.88 (m, 1H, C**H**N), 7.65 (t, J=8.1, 1H, CH^{Qi}), 7.80 (t, J=8.4, 1H, CH^{Qi}), 7.91 (d, J=8.1, 1H, CH^{Qi}), 8.13 (d, J=8.4, 1H, CH^{Qi}), 8.32 (d, J=8.6, 1H, CH^{Qi}), 8.87 (d, J=8.6, 1H, CH^{Qi}), 10.60 (br s, 1H, NH); ^{13}C NMR: δ 27.5 (C(**C**H$_3$)$_3$), 34.9 (**C**(CH$_3$)$_3$), 63.9 (**C**HN), 65.4 (**C**H$_2$O), 122.2, 128.1, 128.5, 129.7, 130.4, 130.7, 137.5, 145.8, 150.6, 192.6 (N**C**=S).

4.2.16. (*R*)-2,6-Pyridine bis[*N*-(2-hydroxy-1-phenylethyl)thiocarboxamide] 21c. Prepared according to the general procedure **A** starting from dithioester **20** and aminoalcohol **3c** (time: 48 h); yellow oil, yield=70%, R_f=0.32 (P/DEE: 30/70); ^{1}H NMR: δ 2.48 (s, 2H, 2×O**H**), 4.08–4.21 (m, 4H, 2×C**H**$_2$O), 5.74 (m, 2H, 2×C**H**N), 7.29–7.43 (m, 5H, C$_6$H$_5$), 7.98 (t, J=7.8, 1H, CH^{Py}), 8.76 (d, J=7.8, 2H, **H**$_3$ and 2×CH^{Py}), 10.65 (d, J=9.5, 2H, 2×N**H**); ^{13}C NMR: δ 60.14 (**C**HN), 66.14 (**C**H$_2$O), 127.29, 127.72, 128.4, 129.35, 137.92, 139.1, 149.53, 190.50 (N**C**=S).

4.2.17. (*S*)-2,6-Pyridine bis[*N*-(1-(hydroxymethyl)-2,2-dimethylpropyl)thiocarboxamide] 21d. Prepared according to the general procedure **A** starting from dithioester **20** and aminoalcohol **3d** (time: 24 h); yellow oil, yield=65%, R_f=0.6 (P/DEE: 50/50); ^{1}H NMR: δ 1.12 (s, 18H, 2×C(C**H**$_3$)$_3$), 1.95 (s, 2H, 2×O**H**), 3.89 (dd, J_1=11.3, J_2=5.5, 1H, C**H**HO), 4.03 (dd, J_1=11.3, J_2=3.4, 1H, CH**H**O), 5.74 (ddd, J_1=9.9, J_2=5.5, J_3=3.4, 2H, 2×C**H**N), 8.01 (t, J=7.8, 1H, CH^{Py}), 8.87 (d, J=7.8, 2H, 2×CH^{Py}), 10.09 (d, J=9.9, 2H, 2×N**H**); ^{13}C NMR: δ 27.7 (2×C(**C**H$_3$)$_3$), 35.4 (2×**C**(CH$_3$)$_3$), 62.9 (**C**HN), 64.5 (**C**H$_2$O), 128.6, 138.8, 149.8, 191.8 (N**C**=S).

4.3. General procedure B for the preparation of thiazolines 6, 7, 12, 13, 16, 19 and 22‡

To a stirred mixture of thioamide (**4**, **5**, **10**, **11**, **15** or **18**, 10 mmol) and mesylchloride (14 mmol) in THF (50 mL) were added dropwise NEt$_3$ (28 mmol) at room temperature. Stirring was maintained for 10 min then water (20 mL) was added and the mixture extracted with dichloromethane (2×20 mL). The organic phase was dried (MgSO$_4$), solvents were evaporated and the residual oil was purified by flash chromatography on silica gel (P/DEE) to provide the thiazoline.

4.3.1. (*R*)-4-Ethyl-2-isopropyl-2-thiazoline 6a. Prepared according to the general procedure **B** starting from thioamide **4a**; yellow oil, yield=92%, R_f=0.69 (P/DEE: 70/30); ^{1}H NMR: δ 0.99 (t, J=7.5, 3H, C**H**$_3$CH$_2$), 1.2 and 1.21 (2d, J=6.9, 6H, HC(C**H**$_3$)$_2$), 1.55–1.92 (m, 2H, CH$_3$C**H**$_2$), 2.80 (sept., J=6.9, 1H, **H**C(CH$_3$)$_2$), 2.90 (dd, J_1=10.8, J_2=7.8, 1H, C**H**HS), 3.30 (dd, J_1=10.8, J_2=8.5, 1H, CH**H**S), 4.36 (m, 1H, C**H**N); ^{13}C NMR: δ 11.0 (CH$_2$**C**H$_3$), 21.5 and 21.6 (CH(**C**H$_3$)$_2$), 28.3 (**C**H$_2$CH$_3$), 34.3 (**C**H(CH$_3$)$_2$), 37.4 (**C**H$_2$S), 78.7 (**C**HN), 175.9 (S–**C**=N).

‡ For the bis-thiazoline **22**, the corresponding stoichiometry was used: bis-thioamide **20** (10 mmol), mesylchloride (28 mmol) and NEt$_3$ (56 mmol).

4.3.2. (*R*)-2,4-Diisopropyl-2-thiazoline 6b. Prepared according to the general procedure **B** starting from thioamide **4b**; yellow oil, yield=98%, R_f=0.95 (P/DEE, 70/30); ^{1}H NMR: δ 0.93 and 1.01 (2d, J=6.8, 6H, CH(C**H**$_3$)$_2$), 1.19 and 1.21 (2d, J=3.2, 6H, C(N)CH(C**H**$_3$)$_2$), 2.01 (sept., J=6.8, 1H, C**H**(CH$_3$)$_2$), 2.97 (dd, J_1=10.9, J_2=8.9, 1H, C**H**HS), 3.22 (dd, J_1=10.9, J_2=8.6, 1H, CH**H**S), 4.26 (m, 1H, C**H**N); ^{13}C NMR: δ 18.4 and 19.4 (CH(CH$_3$)$_2$), 21.1 and 21.3 (C(N)CH(CH$_3$)$_2$), 32.8 (CH(CH$_3$)$_2$), 34.0 (C(N)CH(CH$_3$)$_2$), 34.3 (CH$_2$S), 83.0 (CHN), 175.3 (S–C=N); IR (NaCl): 2960, 2870, 1630 ($\nu_{S-C=N}$), 1460, 1380, 1360.

4.3.3. (*R*)-2-Cyclohexyl-4-ethyl-2-thiazoline 7a. Prepared according to the general procedure **B** starting from thioamide **5a**; yellow oil, yield=98%, R_f=0.78 (P/DEE: 50/50); ^{1}H NMR: δ 0.92 (t, J=7.5, 3H, C**H**$_3$CH$_2$), 1.08–1.97 (m, 12H, CH$_3$C**H**$_2$ and (C**H**$_2$)$_5$), 2.40 (m, 1H, CH), 2.81 (dd, J_1=10.7, J_2=7.8, 1H, C**H**HS), 3.21 (dd, J_1=10.7, J_2=7.7, 1H, CH**H**S), 4.28 (m, 1H, C**H**N); ^{13}C NMR: δ 12.0 (**C**H$_3$CH$_2$), 26.2, 28.4, 32.0, 31.9, 37.2 (**C**H$_2$S), 43.8, 78.6 (**C**HN), 174.9 (S–**C**=N); IR (NaCl): 2920, 2840, 1620 ($\nu_{S-C=N}$), 1450, 1370, 1175.

4.3.4. (*R*)-2-Cyclohexyl-4-isopropyl-2-thiazoline 7b. Prepared according to the general procedure **B** starting from thioamide **5b**; yellow oil, yield=98%, R_f=0.83 (P/DEE: 50/50); ^{1}H NMR: δ 0.92 and 1.01 (2d, J=6.8, 6H, HC(C**H**$_3$)$_2$), 1.08–2.08 (m, 11H, **H**C(CH$_3$)$_2$ and (C**H**$_2$)$_5$), 2.41 (m, 1H), 2.94 (dd, J_1=10.9, J_2=8.6, 1H, C**H**HS), 3.21 (dd, J_1=10.9, J_2=9.0, 1H, CH**H**S), 4.28 (m, 1H, C**H**N); ^{13}C NMR: δ 18.8 and 19.8 (HC(**C**H$_3$)$_2$), 26.2, 31.9, 32.1, 33.3 (H**C**(CH$_3$)$_2$), 34.5 (**C**H$_2$S), 43.9, 83.3 (**C**HN), 174.7 (S–**C**=N); IR (NaCl): 2930, 2860, 1630 ($\nu_{S-C=N}$), 1450, 1340, 1160.

4.3.5. (*R*,*R*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-ethylthiazoline] 12a. Prepared according to the general procedure **B** starting from thioamide **10a**; yellow oil, $[\alpha]_D^{20}$ +161 (*c* 1.3, acetone), yield=98%, R_f=0.53 (P/DEE: 70/30); ^{1}H NMR: δ 1.00 (t, J=7.4, 6H, 2×C**H**$_3$CH$_2$), 1.54 (s, 6H, C(C**H**$_3$)$_2$), 1.57–1.82 (m, 4H, 2×CH$_3$C**H**$_2$), 2.95 (dd, J_1=10.8, J_2=7.1, 2H, 2×C**H**HS), 3.40 (dd, J_1=10.8, J_2=8.6, 2H, 2×CH**H**S), 4.34–4.50 (m, 2H, 2×C**H**N); ^{13}C NMR: δ 11.0 (CH$_2$**C**H$_3$), 27.0 and 27.8 (C(**C**H$_3$)$_2$), 28.4 (CH$_3$**C**H$_2$), 37.9 (**C**H$_2$S), 47.6 (**C**(CH$_3$)$_2$), 78.7 (**C**HN), 173.8 (S–**C**=N); IR (NaCl): 2966, 2930, 2872, 1614 ($\nu_{C=N}$), 1458, 1378 (ν_{CH}), 1162, 1040; MS *m*/*z*: 270 (M$^{+\bullet}$/100), 255 (24), 242 (62), 241 (35), 214 (38), 183 (49), 153 (16), 105 (31), 77 (24), 68 (28), 55 (43), 44 (29). Anal. calcd for C$_{13}$H$_{22}$N$_2$S$_2$: C, 57.73; H, 8.20; N, 10.36; S, 23.71. Found: C, 57.41; H, 8.23; N, 10.31; S, 23.55.

4.3.6. (*R*,*R*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-isopropylthiazoline] 12b. Prepared according to the general procedure **B** starting from thioamide **10b**; yellow oil, $[\alpha]_D^{20}$ +130 (*c* 1, acetone), yield=98%, R_f=0.87 (P/DEE: 70/30); ^{1}H NMR: δ 0.89 and 0.97 (2d, J=6.7, 12H, 2×CH(C**H**$_3$)$_2$), 1.56 (s, 6H, C(C**H**$_3$)$_2$), 2.00–2.10 (m, 2H, 2×C**H**(CH$_3$)$_2$), 3.04 (dd, J_1=10.9, J_2=8.5, 2H,

2×C**H**HS), 3.26 (dd, $J_1=10.9$, $J_2=9.0$, 2H, 2×CH**H**S), 4.23–4.40 (m, 2H, 2×C**H**N); ^{13}C NMR: δ 18.9 and 19.9 (CH(**C**H$_3$)$_2$), 27.1 (C(**C**H$_3$)$_2$), 33.1 (H**C**(CH$_3$)$_2$), 35.5 (**C**H$_2$S), 47.9 (**C**(CH$_3$)$_2$), 83.5 (CHN), 173.6 (S**C**=N); IR (NaCl): 2960, 2870, 1620 ($\nu_{S-C=N}$), 1460, 1380, 1270; HRMS calcd for $C_{15}H_{26}N_2S_2$: 298.1537. Found: 298.1516.

4.3.7. (*R*,*R*)-2,2′-Cyclohexylidenebis[4-ethyl-4,5-dihydrothiazoline] 13a. Prepared according to the general procedure **B** starting from dithioester **11a**; yellow oil, $[\alpha]_D^{20}$ +90 (*c* 1, acetone), yield = 98%, $R_f=0.75$ (P/DEE: 70/30); ^{1}H NMR: δ 0.93 (t, $J=7.4$, 6H, 2×C**H**$_3$CH$_2$), 1.32–2.04 (m, 14H, 2×CH$_3$C**H**$_2$ and (C**H**$_2$)$_5$), 2.86 and 3.22 (dd, $J_1=11.0$, $J_2=8.6$, 2H, 2×C**H**HS), 3.35 (dd, $J_1=11.0$, $J_2=6.7$, 2H, 2×CH**H**S), 4.29–4.48 (m, 2H, 2×C**H**N); ^{13}C NMR: δ 11.0 (**C**H$_3$CH$_2$), 23.1, 25.8, 27.8, 35.7, 37.3 (**C**H$_2$S), 51.8, 78.8 (**C**HN), 173.1 (S–**C**=N); IR (NaCl): 2920, 2840, 1600 ($\nu_{S-C=N}$), 1440, 1370, 1340, 1310; HRMS calcd for $C_{16}H_{26}N_2S_2$: 310.1537. Found: 310.1474.

4.3.8. (*R*,*R*)-2,2′-Cyclohexylidenebis[2-(4,5-dihydro-4-isopropylthiazoline)] 13b. Prepared according to the general procedure **B** starting from thioamide **11b**; yellow oil, $[\alpha]_D^{20}$ +31 (*c* 1, acetone), yield = 98%, $R_f=0.92$ (P/DEE: 70/30); ^{1}H NMR: δ 0.96 and 1.03 (2d, $J=6.8$, 12H, 2×CH(C**H**$_3$)$_2$), 1.41–1.61 and 2.00–2.12 (2m, 12H, 2×C**H**(CH$_3$)$_2$ and (C**H**$_2$)$_5$), 3.01 (dd, $J_1=10.8$, $J_2=8.4$, 2H, 2×C**H**HS), 3.23 (dd, $J_1=10.8$, $J_2=9.0$, 2H, 2×CH**H**S), 4.31–4.48 (m, 2H, 2×C**H**N); ^{13}C NMR: δ 19.0 and 19.9 (CH(**C**H$_3$)$_2$), 23.1, 25.8, 33.1, 34.8 (**C**H$_2$S), 35.7, 51.9, 83.6 (**C**HN), 172.7 (S–**C**=N); IR (NaCl): 2940, 2870, 1610 ($\nu_{S-C=N}$), 1460, 1370, 1270; HRMS calcd for $C_{18}H_{30}N_2S_2$: 338.1850. Found: 338.1859.

4.3.9. 2-[(*R*)-4,5-Dihydro-4-ethyl-2-thiazolyl]pyridine 16a. Prepared according to the general procedure **B** starting from thioamide **15a**; yellow oil, $[\alpha]_D^{20}$ +84 (*c* 1, acetone), yield = 98%, $R_f=0.58$ (P/DEE: 70/30); ^{1}H NMR: δ 1.11 (t, $J=7.5$, 3H, C**H**$_3$CH$_2$), 1.70–2.00 (m, 2H, CH$_3$C**H**$_2$), 3.01 (dd, $J_1=11.0$, $J_2=8.7$, 1H, C**H**HS), 3.48 (dd, $J_1=11.0$, $J_2=8.3$, 1H, CH**H**S), 4.65 (m, 1H, C**H**N), 7.35 (ddd, $J_1=7.5$, $J_2=4.9$, $J_3=1.2$, 1H, CH^{Py}), 7.72 (dt, $J_1=J_2=7.5$, $J_3=1.7$, 1H, CH^{Py}), 8.08 (d, $J=7.9$, 1H, CH^{Py}), 8.65 (d, $J=4$, 1H, CH^{Py}); ^{13}C NMR: δ 11.3 (**C**H$_3$CH$_2$), 28.6 (CH$_3$**C**H$_2$), 36.9 (**C**H$_2$S), 80.1 (**C**HN), 122.1, 125.7, 136.8, 149.6, 151.8, 168.8 (S**C**=N); IR (NaCl): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1460, 1370, 1270; HRMS calcd for $C_{10}H_{12}N_2S$: 192.0721. Found: 192.0752.

4.3.10. 2-[(*R*)-4,5-Dihydro-4-isopropyl-2-thiazolyl]-pyridine 16b. Prepared according to the general procedure **B** starting from thioamide **15b**; orange oil, $[\alpha]_D^{20}$ −54 (*c* 1, acetone), yield = 98%, $R_f=0.81$ (P/DEE: 70/30); ^{1}H NMR: δ 1.05 and 1.13 (2d, $J=6.8$, 6H, HC(C**H**$_3$)$_2$), 2.13 (sept., $J=6.8$, 1H, HC(CH$_3$)$_2$), 3.12 (dd, $J_1=11.0$, $J_2=9.6$, 1H, C**H**HS), 3.39 (dd, $J_1=11.0$, $J_2=9.0$, 1H, CH**H**S), 4.53 (m, 1H, C**H**N), 7.36 (ddd, $J_1=7.5$, $J_2=4.8$, $J_3=1.1$, 1H, CH^{Py}), 7.76 (dt, $J_1=J_2=7.5$, $J_3=1.8$, 1H, CH^{Py}), 8.11 (d, $J=7.4$, 1H, CH^{Py}), 8.59 (d, $J=4.8$, 1H, CH^{Py}); ^{13}C NMR: δ 19.3 and 20.1 (HC(**C**H$_3$)$_2$), 33.8 (H**C**(CH$_3$)$_2$), 34.7 (**C**H$_2$S), 85.0 (**C**HN), 122.0, 125.6, 136.8, 149.6, 151.8, 169.0 (S**C**=N); IR (NaCl): 2960, 2870, 1610 ($\nu_{S-C=N}$), 1470, 1380, 1270; HRMS calcd for $C_{11}H_{14}N_2S$: 206.0878. Found: 206.0855

4.3.11. 2-[(*R*)-4,5-Dihydro-4-phenyl-2-thiazolyl]pyridine 16c. Prepared according to the general procedure **B** starting from thioamide **15c**; yellow solid, mp = 79°C, $[\alpha]_D^{20}$ −89 (*c* 1, acetone), yield = 95%, $R_f=0.38$ (P/DEE: 70/30); ^{1}H NMR: δ 3.31 (dd, $J_1=11.1$, $J_2=9.5$, 1H, C**H**HS), 3.80 (dd, $J_1=11.1$, $J_2=9.1$, 1H, CH**H**S), 5.79 (m, 1H, C**H**N), 7.21–7.45 (m, 6H, CH^{Py} and C$_6$H$_5$), 7.80 (dt, $J_1=J_2=7.7$, $J_3=1.5$, 1H, CH^{Py}), 8.11 (d, $J=7.9$, 1H, CH^{Py}), 8.59 (d, $J=4.6$, 1H, CH^{Py}); ^{13}C NMR: δ 40.4 (**C**H$_2$S), 81.7 (**C**HN), 122.2, 125.9, 127.1, 128.1, 129.2, 136.9, 142.7, 149.7, 151.5, 169.0 (S**C**=N); IR (NaCl): 3050, 2940, 1610 ($\nu_{S-C=N}$), 1490, 1340, 1290; HRMS calcd for $C_{14}H_{12}N_2S$: 240.0721. Found: 240.0746.

4.3.12. 2-[(*R*)-4,5-Dihydro-4-ethyl-2-thiazolyl]quinoline 19a. Prepared according to the general procedure **B** starting from thioamide **18a**; yellow solid, mp = 76°C, $[\alpha]_D^{20}$ +113 (*c* 1, acetone), yield = 95%, $R_f=0.65$ (P/DEE: 30/70); ^{1}H NMR: δ 1.12 (t, $J=7.5$, 3H, C**H**$_3$CH$_2$), 1.73–2.03 (m, 2H, CH$_3$C**H**$_2$), 3.13 (dd, $J_1=11.1$, $J_2=9.1$, 1H, C**H**HS), 3.42 (dd, $J_1=11.1$, $J_2=9.5$, 1H, CH**H**S), 4.72 (m, 1H, C**H**N), 7.57 (ddd, $J_1=8.0$, $J_2=6.9$, $J_3=1.2$, 1H, H^{Qi}), 7.73 (ddd, $J_1=8.4$, $J_2=6.9$, $J_3=1.5$, 1H, H^{Qi}), 8.82 (d, $J=8.0$, 1H, H^{Qi}), 8.16–8.19 (m, 3H, H^{Qi}); ^{13}C NMR: δ 11.44 (**C**H$_3$CH$_2$), 28.7 (CH$_3$**C**H$_2$), 36.9 (**C**H$_2$S), 80.5 (**C**HN), 119.3, 127.9, 128.0, 129.2, 130.2, 130.5, 136.8, 148.0, 152.0, 169.9 (N**C**=S); IR (KBr): 3060, 2860, 1590 ($\nu_{S-C=N}$), 1560, 1500, 1430, 1374, 1280, 1090; HRMS calcd for $C_{14}H_{14}N_2S$: 242.0878. Found: 242.0858.

4.3.13. 2-[(*R*)-4,5-Dihydro-4-isopropyl-2-thiazolyl]-quinoline 19b. Prepared according to the general procedure **B** starting from thioamide **18b**; yellow solid, mp = 88°C, $[\alpha]_D^{20}$ +115 (*c* 1, acetone), yield = 95%, $R_f=0.80$ (P/DEE: 30/70); ^{1}H NMR: δ 1.08 and 1.18 (2d, $J=6.8$, 6H, HC(C**H**$_3$)$_2$), 2.18 (m, 1H, H**C**(CH$_3$)$_2$), 3.17 (dd, $J_1=10.9$, $J_2=9.6$, 1H, C**H**HS), 3.44 (dd, $J_1=10.9$, $J_2=9.0$, 1H, CH**H**S), 4.60 (m, 1H, C**H**N), 7.60 (ddd, 1H, $J_1=8.0$, $J_2=6.9$, $J_3=1.1$, 1H, H^{Qi}), 7.76 (ddd, $J_1=8.4$, $J_2=6.9$, $J_3=1.4$, 1H, H^{Qi}), 8.85 (dd, $J_1=8.0$, $J_2=1.2$, 1H, H^{Qi}), 8.19–8.24 (m, 3H, H^{Qi}); ^{13}C NMR: δ 19.4 and 20.2 (HC(**C**H$_3$)$_2$), 33.9 (H**C**(CH$_3$)$_2$), 34.7 (**C**H$_2$S), 85.2 (**C**HN), 119.4, 127.9, 128.0, 129.2, 130.1, 130.5, 136.7, 148, 151.8, 177.9 (N**C**=S); IR (KBr): 3050, 2860, 1590 ($\nu_{S-C=N}$), 1500, 1460, 1340, 1305, 1090; HRMS calcd for $C_{15}H_{16}N_2S$: 256.1034. Found: 256.1056.

4.3.14. 2-[(*R*)-4,5-Dihydro-4-phenyl-2-thiazolyl]quinoline 19c. Prepared according to the general procedure **B** starting from thioamide **18c**; white solid, mp = 132°C, $[\alpha]_D^{20}$ +30 (*c* 1, acetone), yield = 95%, $R_f=0.45$ (P/DEE: 70/30); ^{1}H NMR: δ 3.35 (dd, $J_1=11.2$, $J_2=9.6$, 1H, C**H**HS), 3.89 (dd, $J_1=11.2$, $J_2=9.1$, 1H, CH**H**S), 5.85 (m, 1H, C**H**N), 7.15–7.40 (m, 5H, C$_6$H$_5$), 7.6 (ddd, $J_1=8.0$, $J_2=6.95$, $J_3=1.1$, 1H, H^{Qi}), 7.76 (ddd, $J_1=8.2$,

$J_2=6.95$, $J_3=1.5$, 1H, H^{Qi}), 8.82 (d, $J=8.0$, 1H, H^{Qi}), 8.22–8.31 (m, 3H, H^{Qi}); ^{13}C NMR: δ 40.1 (**C**H_2S), 81.7 (**C**HN), 119.3, 127.0, 128.0, 129.2, 128.1, 128.2, 129.2, 130.3; 130.5, 136.9, 142.4, 148.0, 151.5, 172.1 (N**C**=S); IR (KBr): 3020, 2900, 1590 ($\nu_{S-C=N}$), 1490, 1450, 1310. Anal. calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 74.13; H, 4.82; N, 9.73; S, 10.68.

4.3.15. 2-[(*S*)-4,5-Dihydro-4-*tert*-butyl-2-thiazolyl]-quinoline 19d. Prepared according to the general procedure **B** starting from thioamide **18d**; white solid, mp = 118°C, $[\alpha]_D^{20}$ −90 (*c* 1, acetone), yield = 90%, $R_f=0.87$ (P/DEE: 70/30); ^1H NMR: δ 1.09 (s, 9H, C(C**H**$_3)_3$), 3.22 (t, $J_1=J_2=10.9$, 1H, C**H**HS), 3.35 (dd, $J_1=10.9$, $J_2=9.2$, 1H, CH**H**S), 4.51 (dd, $J_1=10.9$, $J_2=9.2$, 1H, C**H**N), 7.58 (ddd, $J_1=8.1$, $J_2=7.4$, $J_3=0.9$, 1H, H^{Qi}), 7.73 (ddd, $J_1=8.4$, $J_2=6.9$, $J_3=1.4$, 1H, H^{Qi}), 8.83 (dd, $J_1=8.1$, $J_2=1.4$, 1H, H^{Qi}), 8.17–8.24 (m, 3H, H^{Qi}); ^{13}C NMR: δ 27.3 (C(**C**H$_3)_3$), 33.3 (**C**H$_2$S), 34.7 (**C**(CH$_3)_3$), 88.9 (**C**HN), 119.4, 127.9, 128.0, 129.2, 130.1, 130.5, 136.7, 148, 151.9, 169.4 (N**C**=S); IR (KBr): 2950, 2860, 1600 ($\nu_{S-C=N}$), 1500, 1460. Anal. calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 71.15; H, 6.86; N, 10.19; S, 11.72.

4.3.16. (*R*,*R*)-2,6-Bis[4-diphenyl-4,5-dihydro-2-thiazoline]pyridine 22c. Prepared according to the general procedure **B** starting from thioamide **21c**; white solid, mp = 212°C, $[\alpha]_D^{20}$ +49 (*c* 1, acetone), yield = 69%, $R_f=0.78$ (P/DEE: 70/30); ^1H NMR: δ 3.48 (dd, $J_1=11.1$, $J_2=9.6$, 2H, 2×C**H**HS), 3.54 (dd, $J_1=11.1$, $J_2=9.1$, 2H, 2×CH**H**S), 5.81–5.92 (m, 2H, 2×**C**HN), 7.32–7.5 (m, 10H, 2×C_6H_5), 7.87 (t, $J=7.8$, 1H, H^{Py}), 8.27 (d, $J=7.8$, 2H, H^{Py}); ^{13}C NMR: δ 40.2 (**C**H_2S), 81.9 (**C**HN), 123.7, 127.0, 128.2, 129.18, 142.1, 151.0, 177.2 (N**C**=S); IR (KBr): 2930, 2906, 1600 ($\nu_{S-C=N}$), 1450, 1260, 1114, 1018; HRMS calcd for $C_{23}H_{29}N_3S_2$: 401.102. Found: 401.1001.

4.3.17. (*S*,*S*)-2,6-Bis[4-(1,1-dimethylethyl)-4,5-dihydro-2-thiazoline]pyridine 22d. Prepared according to the general procedure **B** starting from thioamide **21d**; white solid, mp = 198°C, $[\alpha]_D^{20}$ −123 (*c* 1, acetone), yield = 70%, $R_f=0.60$ (P/DEE: 75/25); ^1H NMR: δ 1.08 (s, 18H, C(C**H**$_3)_3$), 3.21 (t, $J_1=J_2=10.9$, 2H, 2×C**H**HS), 3.32 (dd, $J_1=10.9$, $J_2=9.3$, 2H, 2×CH**H**S), 4.45 (dd, $J_1=10.9$, $J_2=9.3$, 2H, 2×**C**HN), 7.83 (t, $J=7.8$, 1H, H^{Py}), 8.18 (d, $J=7.8$, 2H, H^{Py}); ^{13}C NMR: δ 27.1 (**C**(CH$_3)_3$), 33.0 (**C**H$_2$S), 36.0 (**C**(CH$_3)_3$), 88.1 (**C**HN), 123.8, 137.5, 150.6, 177.9 (N**C**=S); IR (KBr): 2950, 2860, 1612 ($\nu_{S-C=N}$), 1460, 1360; HRMS calcd for $C_{21}H_{37}N_3S_2$: 361.1646. Found: 361.1680.

4.4. General procedure C for the preparation of dithioesters thiazolines 8 and 9

In a dry two-necked round-bottomed flask, under nitrogen, was introduced a solution of thiazoline (**4** or **5**, 10 mmol) in freshly distillated THF (20 mL), cooled to −78°C. A solution of *t*-BuLi (1.8 M in cyclohexane) was then added dropwise and the mixture was stirred for 3 h. Carbon disulfide (30 mmol) was then slowly added at −40°C. The resulting brown solution was stirred at this temperature for 2 h and then methyl iodide (30 mmol, 3 equiv.) was added at −10°C. The resulting dark red solution was allowed to react overnight at room temperature and then poured into water. The mixture was extracted twice with 100 mL of diethyl ether. Organic layers were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude oil was purified over silica gel (P/DEE).

4.4.1. (*R*)-Methyl-2-methyl-2-(4-ethyl-4,5-dihydro-2-thiazolyl)propanedithioate 8a. Prepared according to the general procedure **C** starting from the thiazoline **6a**; orange oil, yield = 85%, $R_f=0.44$ (P/DEE: 95/5); ^1H NMR: δ 1.02 (t, $J=7.5$, 3H, CH$_2$C**H**$_3$), 1.63–1.84 (m, 2H, C**H**$_2$CH$_3$), 1.74 (s, 6H, C(C**H**$_3)_2$), 2.61 (s, 3H, SC**H**$_3$), 2.99 (dd, $J_1=10.8$, $J_2=8.8$, 1H, C**H**HS), 3.35 (dd, $J_1=10.8$, $J_2=8.7$, 1H, CH**H**S), 4.48 (m, 1H, C**H**N); ^{13}C NMR: δ 11.1 (CH$_2$**C**H$_3$), 21.0 (**C**H$_3$S), 27.7 (**C**H$_2$CH$_3$), 30.1 and 30.2 (C(**C**H$_3)_2$), 38.2 (**C**H$_2$S), 60.4 (**C**(CH$_3)_2$), 78.6 (**C**HN), 173.5 (S–**C**=N), 242.8 (**C**=S).

4.4.2. (*R*)-Methyl-2-methyl-2-(4,5-dihydro-4-isopropyl-2-thiazolyl)propanedithioate 8b. Prepared according to the general procedure **C** starting from the thiazoline **6b**; orange oil, yield = 83%, $R_f=0.5$ (P/DEE: 95/5); ^1H NMR: δ 0.97 and 1.03 (2d, $J=6.8$, 6H, CH(C**H**$_3)_2$), 1.74 (s, 6H, C(C**H**$_3)_2$), 2.09 (m, 1H, C**H**(CH$_3)_2$), 2.61 (s, 3H, C**H**$_3$S), 3.02 (dd, $J_1=10.8$, $J_2=8.8$, 1H, C**H**HS), 3.27 (dd, $J_1=10.8$, $J_2=8.7$, 1H, CH**H**S), 4.32 (m, 1H, C**H**N); ^{13}C NMR: δ 19.0 and 20.0 (CH(**C**H$_3)_2$), 20.9 (**C**H$_3$S), 30.0 and 30.2 (C(**C**H$_3)_2$), 33.0 (**C**H(CH$_3)_2$), 35.7 (**C**H$_2$S), 60.6 (**C**(CH$_3)_2$), 83.4 (**C**HN), 173.1 (S–**C**=N), 243.1 (**C**=S); IR (NaCl): 2960, 2870, 1620 ($\nu_{S-C=N}$), 1460, 1090 ($\nu_{C=S}$).

4.4.3. (*R*)-Methyl-1-(4-ethyl-4,5-dihydro-2-thiazolyl)-cyclohexanedithiocarboxylate 9a. Prepared according to the general procedure **C** starting from the thiazoline **7a**; orange oil, yield = 82%, $R_f=0.48$ (P/DEE: 90/10); ^1H NMR: δ 1.03 (t, $J=7.4$, 3H, CH$_2$C**H**$_3$), 1.52–2.49 (m, 12H, C**H**$_2$CH$_3$ and (C**H**$_2)_5$), 2.59 (s, 3H, SC**H**$_3$), 2.95 (dd, $J_1=10.8$, $J_2=6.8$, 1H, C**H**HS), 3.32 (dd, $J_1=10.8$, $J_2=8.5$, 1H, CH**H**S), 4.52 (m, 1H, CHN); ^{13}C NMR: δ 11.21 (CH$_2$**C**H$_3$), 20.86 (**C**H$_3$S), 23.46, 23.50, 25.66, 27.69 (CH$_2$CH$_3$), 37.54, 38.28 (SCH$_2$), 64.59, 78.92 (CHN), 171.85 (SC=N), 243.5 (C=S); IR (NaCl): 2840, 2910, 1600 ($\nu_{S-C=N}$), 1440, 1230, 1200, 1115 ($\nu_{C=S}$).

4.4.4. (*R*)-Methyl-1-(4,5-dihydro-4-isopropyl-2-thiazolyl)-cyclohexanedithiocarboxylate 9b. Prepared according to the general procedure **C** starting from the thiazoline **7b**; orange oil, yield = 79%, $R_f=0.46$ (P/DEE: 90/10); ^1H NMR: δ 0.98 and 1.05 (2d, $J=6.8$, 6H, CH(C**H**$_3)_2$), 1.25–2.50 (m, 11H, (C**H**$_2)_5$ and C**H**(CH$_3)_2$), 2.59 (s, 3H, C**H**$_3$S), 3.01 (dd, $J_1=10.8$, $J_2=8.8$, 1H, C**H**HS), 3.22 (dd, $J_1=10.8$, $J_2=8.9$, 1H, CH**H**S), 4.32 (m, 1H, C**H**N); ^{13}C NMR: δ 19.2 and 20.1 (CH(**C**H$_3)_2$), 20.8 (**C**H$_3$S), 23.5, 25.7, 33.0 (**C**H(CH$_3)_2$), 35.1 (**C**H$_2$S), 38.3, 38.5, 64.7 (**C**(CH$_3)_2$), 83.8 (**C**HN), 171.3 (S–**C**=N), 243.1 (**C**=S); IR (NaCl): 2850, 2930, 1610 ($\nu_{S-C=N}$), 1450, 1124 ($\nu_{C=S}$).

4.5. Preparation of 2,6-pyridyl di(methylthiocarboxylate) 20

Prepared according to a general method of the literature[4] using 2,6-di(chloromethyl) pyridine (1.42 mmol, 0.25 g), sulfur S_8 (12.8 mmol, 0.41 g), triethylamine (12.8 mmol, 1.8 mL), dimethylformamide (4 mL) and methyl iodide (2.8 mmol, 0.8 mL); dark red needles, mp = 140°C, yield = 40%, $R_f = 0.3$ (P: 100); ^{1}H NMR: δ 2.80 (s, 6H, 2×SC**H**$_3$), 7.89 (t, 1H, $J_1 = J_2 = 7.9$, **H**$_4$), 8.54 (d, 2H, $J_1 = J_2 = 7.9$, **H**$_3$, **H**$_5$); ^{13}C NMR: δ 20.4 (**C**H$_3$S), 125.1, 138.0, 154.0, 227.1 (**C**=S); IR (KBr): 1398, 1102, 1056 ($\nu_{C=S}$).

4.6. Typical procedure for the enantioselective allylation

Under a nitrogen atmosphere, allylpalladium chloride dimer (4.5 mg, 0.0125 mmol), the ligand **12a** (0.0125 mmol) and solid potassium acetate (5 mg, 0.05 mmol) were mixed in 2 mL of toluene for 30 min. Diphenylpropenyl acetate (128 mg, 0.5 mmol) was then added, followed by *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (250 μL, 1 mmol) and the dimethyl malonate (115 μL, 1 mmol). The reaction mixture was stirred for 3 days at 20°C. The solvent was removed and the residue purified on silica gel (P/DEE: 75/25) to afford (*E*)-methyl 2-methoxycarbonyl-3,5-diphenylpent-4-enoate in 90% yield. Enantiomeric excess was measured by HPLC using a Chiralpak AD analytical column Daicel (90/10 *n*-hexane/2-propanol, flow rate 1 mL/min, 251.3 nm). The HPLC separation was calibrated using racemic product ((*S*): $t_1 = 10.5$ min, (*R*): $t_2 = 14.4$ min).

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