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The application of chiral amino thiols as catalysts in the enantioselective addition of diethylzinc to aldehydes

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Abstract—Starting from (*S*)-(−)-valine, a series of new chiral amino thiol and corresponding thioacetate ligands were prepared in an efficient manner and applied in the asymmetric diethylzinc addition to aldehydes with excellent enantioselectivity as high as 99% ee and with a catalytic loading as little as 0.02 mol% of the amino thiol **11c**.

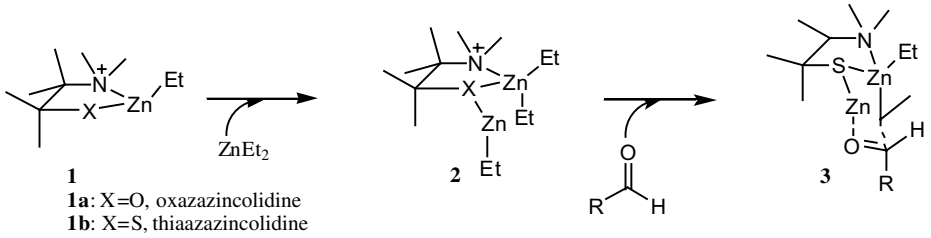
1. Introduction

The enantioselective addition of organozinc reagents to aldehydes catalyzed by enantiopure β-amino alcohols still remains a prime objective as evidenced by many research papers and comprehensive review articles.[1–5] Compared to the amino alcohols as ligands, there are only very limited sources of amino thiols available in the literature for studies on the catalytic ability in the diethylzinc addition to aldehydes.[6–8] Kang et al. reported a few chiral tertiary amino thiols synthesized from (1*R*,2*S*)-1,2-diphenyl-2-amino-1-ethanol and (1*R*,2*S*)-(−)-norephedrine the asymmetric addition of diethylzinc to aldehydes.[8] Jin et al. found that optically active amino thioacetate derivatives of (+)-norephedrine also have shown excellent catalytic properties in such stereoselective additions.[8d] Herein, we report a series of chiral *N*,*S*-type ligands prepared from (*S*)-(−)-valine exhibiting very high efficiency as the catalyst not only in terms of stereoselectivity but more importantly, with a very low catalyst loading of 0.02 mol% (Table 1, entry 11, S (substrata)/C (catalyst) = 5000).

2. Results and discussion

2.1. Synthesis of ligands

In general, the chiral *N*,*N*-dibenzylamino alcohols **6** were prepared from (−)-valine according to the method of Reetz.[9] A typical synthetic sequence for the preparation of the chiral amino thiols **11** is illustrated in Scheme 2. The synthesis began with the *N*,*N*-dialkylation of (*S*)-(−)-valine **4** using benzyl chloride in the presence of NaOH to give the *N*,*N*-dibenzylamino benzyl ester, which was reduced by lithium aluminum hydride to afford the optically active amino primary alcohols. After the Swern oxidation of the amino alcohols,



Scheme 1. Proposed fragments of transition state for the $ZnEt_2$ to aldehyde.

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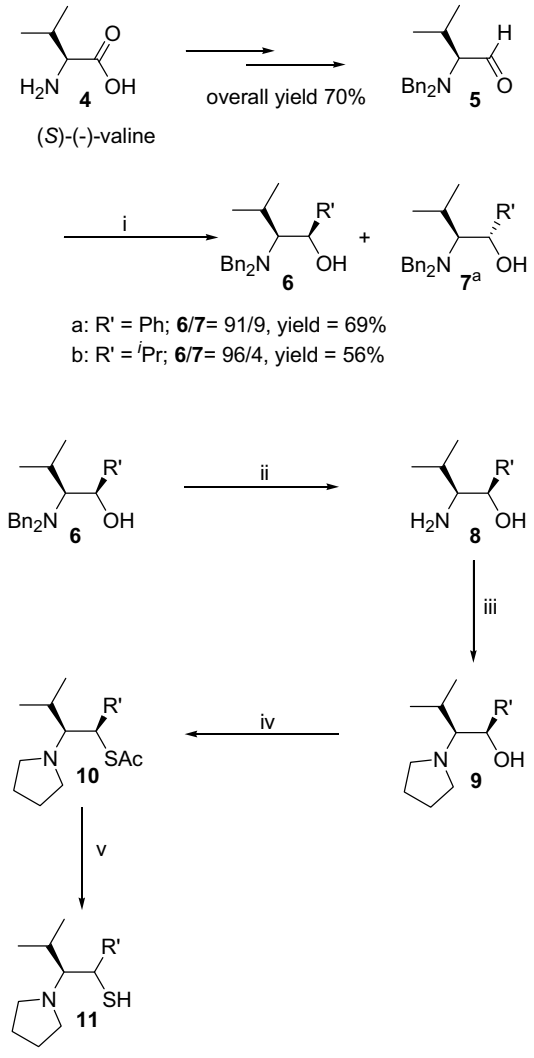
phenylmagnesium bromide or isopropylmagnesium bromide was added to the corresponding aldehydes **5** to give amino alcohols **6** in a high diastereoselectivity. The protecting benzyl group was then removed through hydrogenolysis either by Pd/C or Pd $(OH)_2$ under hydrogen at 1 atm. The dialkylation of the nitrogen in **8** was then carried out with 1,4-dibromobutane to produce tertiary amino alcohol **9**, which was transformed into the mesylate followed by an in situ intramolecular nucleophilic attack by ring nitrogen atom, to furnish the intermediate aziridinium ion with inversion of configuration.[10] This aziridinium ion then underwent regioselective ring opening at the benzylic position by thioacetate to afford amino thioacetate **10**, while retaining the original configuration of **9** through one more inversion. Amino thiol **11** was obtained by the reduction of thioacetate with lithium aluminum hydride.



Scheme 2. New amino thiol chiral ligands with two stereocenters from (*S*)-(−)-valine. Reagents and conditions: (i) R′MgX, THF, 0 °C, 1 h, (ii) H_2, Pd/C, MeOH, 1 atm, rt, 8 h, 92%, (iii) 1,4-dibromobutane, K_2CO_3, CH_3CN, reflux, 18 h, 82–89%, (iv) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C, 1 h then removed CH_2Cl_2, and added AcSH, NEt_3, benzene, reflux, 8 h, 62–69%, (v) LAH, Et_2O, 0 °C, 1 h, 92%. [a]Diastereomeric ratio was determined by ^1H NMR (400 MHz, Varian Mercury 400) spectroscopy.

2.2. Catalysis

The β-amino alcohol ligands possess the inherent properties of acting as a Lewis base to activate the organozinc reagents and also as a Lewis acid to activate the carbonyl substrates. In this context we herein report the results of the superior performance of chiral β-amino thiol synthesized from commercially available natural amino acid namely (*S*)-(−)-valine in comparison to the corresponding amino alcohol. Here we have exploited the softness of sulfur (thiol) showing a greater affinity to the zinc atom when compared to the oxygen atom according to the hard soft acid base (HSAB) rule (Figs. 1 and 3).[8b] Accordingly all thiols **11** and thioacetates **10** we studied showed better selectivity than the corresponding amino alcohol **9** (Fig. 3). Lowering the reaction temperature from 0 to −40 °C (Fig. 2) was found to have no influence on the enantioselectivity of the products formed. We also found the stoichiometry of $ZnEt_2$ used from 1.2 to 5 equiv resulted in only less than 0.3% ee variation under identical conditions of diethylzinc addition to benzaldehyde with two amino thiols **11a** (Table 1, entries 14, 26–29) and **11c** (Table 1, entries 35–40), and that the isolated yields were always above 90%. Hence, all further studies were carried out at −20 °C with 1.2 equiv $ZnEt_2$ in the presence of 5 mol% chiral ligands so as to have a parallel comparison.

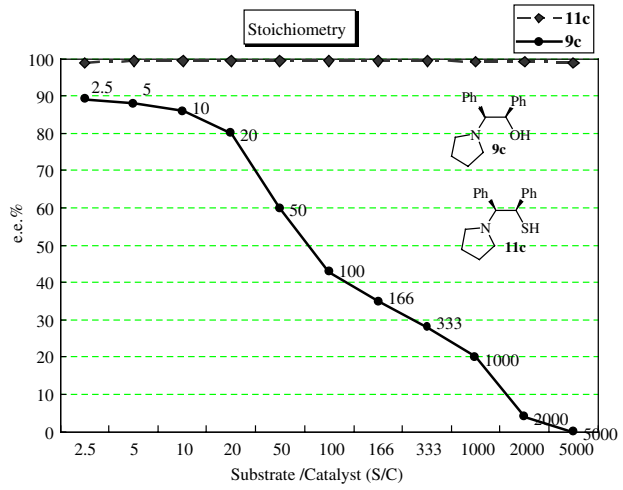


Figure 1. The stoichiometric study of amino thiol **11c** and amino alcohol **9c** in the diethylzinc addition to benzaldehyde.

A very interesting result was observed in the stoichiometric study of the chiral ligand; we found the efficiency was extremely high for amino thiols as a chiral catalyst. For example, the highest ee of 99.5% was obtained with 20 mol% of **11c**, while the ee could still reach as high as 99% (Table 1, entries 2 vs 11) even when the quantity of **11c** was reduced 1000 times to 0.02 mol% (Fig. 1). This is by far the highest S/C ratio ever reported in the literature for an asymmetric addition of $ZnEt_2$ to aldehydes. As the lone pair of electrons on oxygen in THF interfere with the coordination complex **3** formed (Scheme 1) between the ligand, diethylzinc and the aldehyde, the optical selectivity went down to 92.1% ee (Table 1, entry 21).

Table 1. Diethylzinc addition to benzaldehyde catalyzed by amino thiols **11a** and **11c** and amino thiolacetate **10a**

Entry	Ligand	S/C	$ZnEt_2$	Temperature	Time (h)	Add:Red[a]	Ee (%)[b]
1	**11c**	2.5	3.7	−20	12	1:0	98.8 *R*
2	**11c**	5	3.7	−20	12	1:0	99.5 *R*
3	**11c**	10	3.7	−20	12	1:0	99.5 *R*
4	**11c**	20	3.7	−20	12	1:0	99.4 *R*
5	**11c**	50	3.7	−20	12	1:0	99.4 *R*
6	**11c**	100	3.7	−20	12	1:0	99.3 *R*
7	**11c**	166	3.7	−20	12	1:0	99.3 *R*
8	**11c**	333	3.7	−20	12	1:0	99.3 *R*
9	**11c**	1000	3.7	−20	12	1:0.01	99.2 *R*
10	**11c**	2000	3.7	−20	12	1:0.03	99.1 *R*
11	**11c**	5000	3.7	−20	12	1:0.06	99.0 *R*
12	**11a**	2	1.2	−20	12	1:0	99.6 *R*
13	**11a**	5	1.2	−20	12	1:0	99.6 *R*
14	**11a**	20	1.2	−20	12	1:0	99.6 *R*
15	**11a**	1000	1.2	−20	12	1:0.03	99.2 *R*
16	**11a**	2000	1.2	−20	12	1:0.05	98.5 *R*
17	**11a**	10000	1.2	−20	12	1:0.07	96.5 *R*
18	**11a**	20	1.2	rt	6	1:0	98.5 *R*
19	**11a**	20	1.2	0	12	1:0	99.3 *R*
20	**11a**	20	1.2	−20	12	1:0	99.2 *R*[c]
21	**11a**	20	1.2	−20	12	1:0	92.1 *R*[d]
22	**11a**	20	1.2	−20	12	1:0	99.5 *R*[e]
23	**11a**	20	1.2	−20	12	1:0	99.6 *R*[f]
24	**11a**	20	1.2	−40	12	1:0.02	99.7 *R*
25	**11a**	20	1.2	−78	12	1:0.07	90.2 *R*
26	**11a**	20	2	−20	12	1:0	99.6 *R*
27	**11a**	20	3	−20	12	1:0	99.5 *R*
28	**11a**	20	4	−20	12	1:0	99.5 *R*
29	**11a**	20	5	−20	12	1:0	99.5 *R*
30	**11c**	20	1.2	rt	6	1:0	99.1 *R*
31	**11c**	20	1.2	0	9	1:0	99.2 *R*
32	**11c**	20	1.2	−20	12	1:0	99.3 *R*
33	**11c**	20	1.2	−40	12	1:0.03	99.5 *R*
34	**11c**	20	1.2	−78	24	1:0.07	94.2 *R*
35	**11c**	10	1.2	−20	12	1:0	99.3 *R*
36	**11c**	10	2	−20	12	1:0	99.3 *R*
37	**11c**	10	3	−20	12	1:0	99.4 *R*
38	**11c**	10	3.7	−20	12	1:0	99.5 *R*
39	**11c**	10	4	−20	12	1:0	99.5 *R*
40	**11c**	10	5	−20	12	1:0	99.3 *R*
41	**10a**	2	1.2	−20	12	1:0	99.6 *R*
42	**10a**	5	1.2	−20	12	1:0	99.7 *R*
43	**10a**	10	1.2	−20	12	1:0	99.6 *R*
44	**10a**	20	1.2	−20	12	1:0	99.6 *R*
45	**10a**	100	1.2	−20	12	1:0	99.5 *R*
46	**10a**	200	1.2	−20	12	1:0.02	99.5 *R*
47	**10a**	1000	1.2	−20	12	1:0.03	99.3 *R*
48	**10a**	2000	1.2	−20	12	1:0.05	98.7 *R*
49	**10a**	3333	1.2	−20	12	1:0.06	97.7 *R*
50	**10a**	10000	1.2	−20	12	1:0.07	96.0 *R*

[a] The add./red. ratios were determined by ^{1}H NMR. (400 MHz, or 600 MHz, Varian) spectroscopy analysis.
[b] Determined by HPLC (Chiralcel OD column, eluent is *n*-hexane–*i*-propanol = 98:2, flow rate is 1.5 mL/min).
[c] Hexane.
[d] T (Toluene)/THF = 1:1.
[e] T/CH_2Cl_2 = 1:1.
[f] T/benzene = 1:1.

Thus the less polar solvents without a coordinating atom like toluene, hexane, dichloromethane or benzene are much more favored with the ee up to 99.6% (Table 1, entries 14, 20, 22, 23).[11]

The results of the asymmetric diethylzinc addition to various aldehydes in the presence of chiral ligand **11a** are summarized in Table 2. High ee values were obtained in almost all cases. Among them, the aromatic aldehydes gave higher enantiomeric excesses than the aliphatic aldehydes. The electron-donating substitution on the aromatic aldehydes (*o*- and *p*-methoxybenzaldehyde) provided slightly lower ee values than the parent system by lowering the reactivity of carbonyl group

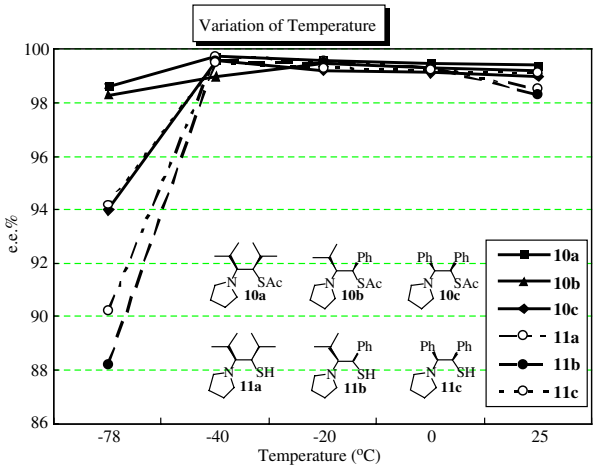


Figure 2. Variation of temperature with different chiral ligands.

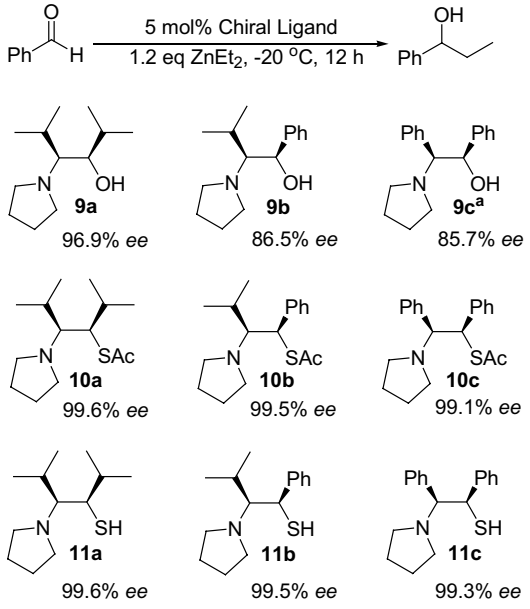


Figure 3. Enantioselective addition of diethylzinc to PhCHO with various chiral ligands. [a]Compound **9c** was synthesized from (1*R*,2*S*)-1,2-diphenyl-2-amino-1-ethanol.

(Table 2, entries 3 and 4 vs 1) while *p*-chlorobenzaldehyde gave a similar ee as that of benzaldehyde.

3. Conclusion

In summary, we have developed a series of new chiral amino thiols and amino thioacetate ligands as pure diastereomers from commercially available amino acid (*S*)-(−)-valine. The amino thiols have been shown to be superior over the corresponding amino alcohol ligands due to the high catalytic ability originating from the softness of sulfur, and we have demonstrated their extremely high efficiency in catalytic asymmetric diethylzinc additions to aldehydes.

4. Experimental

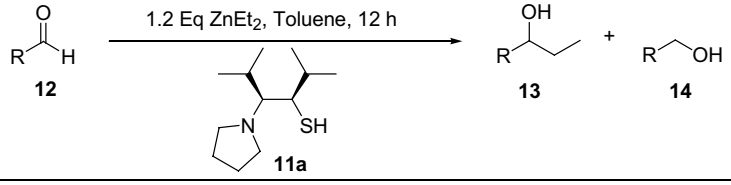
4.1. General procedure for diethylzinc to aldehyde

A typical procedure for the present catalytic reaction is described as follows: Diethylzinc (1.1 M in toluene, 1.2 mmol) was added to a solution of chiral amino thiol **11a** (11.5 mg, 0.05 mmol) in toluene (0.5 mL) at room temperature (20 min). The aldehyde (1 mmol) was added dropwise at −20 °C to the above solution and the reaction mixture then stirred at −20 °C for 12 h until the reaction was complete as judged by TLC analysis, at which point the reaction was quenched at −20 °C by the addition of 1 M HCl. The aqueous phase was extracted with ethyl acetate and the combined extracts dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired alcohol **13**. The product was identified by comparing the ^{1}H NMR and HPLC (Chiralcel OD column).

4.2. (3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexan-3-ol 9a

To a mixture of (3*R*,4*S*)-4-amino-2,5-dimethylhexan-3-ol **8** (5 mmol, 0.75 g) and potassium carbonate (10 mmol,

Table 2. Diethylzinc addition to various aldehydes in the presence of 5 mol% **11a** at −20 °C



Entry	R, **12**	Conversion (%)	**13**:**14**[a]	Ee (%)[b]
1	Phenyl	100	1:0	99.6 (*R*)
2	2-Naphthyl	100	1:0	99.4 (*R*)
3	*o*-$MeOC_6H_4$	100	1:0	95.2 (*R*)
4	*p*-$MeOC_6H_4$	65	1:0.01	96.0 (*R*)
5	*p*-ClC_6H_4	100	1:0	99.6 (*R*)
6	Cyclohexyl	86	1:0.03	90.6 (*R*)[c]
7	*n*-Octyl	92	1:0	91.6 (*R*)[c]

[a] The ratio of add **13** and red **14** were determined by ^{1}H NMR (400 MHz, Varian Mercury 400) spectroscopy.
[b] Determined by HPLC (Chiralcel OD column, eluent is *n*-hexane–*i*-propanol = 98:2, flow rate is 1.5 mL/min).
[c] Determined by GC (Chrompack Chirasil-Dex CB 25 M × 0.25 mm column, nitrogen as carrier gas).

1.4 g) in 40 mL of acetonitrile was added 1,4-dibromobutane (6 mmol, 1.3 g). The solution was then heated to reflux for 18 h, after which the TLC analysis of the reaction mixture indicated the completion of the reaction. The resulting solution was filtered and acetonitrile evaporated. After removal of acetonitrile, 30 mL of water was added to the residual oil then extracted with 3×30 mL of ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude product, which was purified through column chromatography on silica gel to afford (3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl) hexan-3-ol **9a** (0.84 g, 84%) as a colorless oil; $[\alpha]_D^{25} = +45.7$ (*c* 1.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, $J = 6.8$ Hz, 3H, NCHCH(CH_3)$_2$), 0.97 (d, $J = 6.8$ Hz, 3H, NCH-CHCH_3), 1.02 (d, $J = 1.2$ Hz, 3H, OCCHCH_3), 1.04 (d, $J = 1.2$ Hz, 3H, OCCHCH_3), 1.63–1.73 (m, 4H, NCH_2), 1.74–1.83 [m, 1H, NCC*H*(CH_3)$_2$], 2.05–2.12 [m, 1H, OCC*H*(CH_3)$_2$], 2.21 (dd, $J = 3.2$, 4.0 Hz, 1H, NC*H*), 2.55–2.63 (m, 2H, NCH_2), 2.65–2.72 (m, 2H, NCH_2), 3.41 (dd, $J = 4.4$, 9.2 Hz, 1H, C*H*O); ^{13}C NMR(100 MHz, $CDCl_3$) δ 19.20, 19.30, 19.62, 22.68, 23.40, 26.99, 30.59, 51.59, 68.34, 77.60.

4.3. (*S*)-(3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexan-3-yl ethanethioate 10a

To a vigorously stirred solution of (3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl)hexan-3-ol **9a** (4.0 mmol, 0.8 g), Et_3N (12 mmol, 1.8 mL) in 30 mL anhydrous CH_2Cl_2 at 0 °C was added MsCl (8 mmol, 0.62 mL). The resulting solution was stirred for 1 h at 0 °C, after the TLC analysis of the reaction mixture indicated the completion of reaction, then CH_2Cl_2 was removed in vacuum. To the residue was added benzene (30 mL) and NEt_3 (12 mmol, 1.8 mL) and thioacetic acid (8 mmol, 0.57 mL) and then heated to reflux for 8 h while monitoring the completion of reaction by TLC. After removal of solvent, the residued oil was purified through column chromatography (eluent: *n*-hexane–NEt_3 = 100:1) on silica gel to afford (*S*)-(3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl) hexan-3-yl ethanethioate **10a** (0.66 g, 64%) as a colorless oil; $[\alpha]_D^{25} = +53.9$ (*c* 1.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 [d, $J = 6.8$ Hz, 3H, NCHCH(CH_3)$_2$], 0.90–0.98 (m, 9H, CH_3), 1.66–1.71 (m, 4H, CCH_2), 1.88–2.00 [m, 1H, NCC*H*(CH_3)], 2.01–2.12 (m, 1H, SCC*H*Me$_2$), 2.34 (s, 3H, SCO*Me*), 2.62–2.70 (m, 2H, NCH_2), 2.62–2.70 (m, 1H, NC*H*), 2.71–2.77 (m, 2H, NCH_2), 3.79 (dd, $J = 5.2$, 6.4 Hz, 1H, C*H*S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.63, 19.99, 21.11, 21.60, 24.02, 30.45, 30.55, 30.71, 49.25, 50.81, 64.74, 195.38.

4.4. (3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexane-3-thiol 11a

To a suspension solution of LAH (4 mmol, 0.16 g) in 10 mL of dry Et_2O in an ice bath, then a solution of (*S*)-(3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl)hexan-3-yl ethanethioate **10a** (2 mmol, 0.52 g) in 20 mL of dry Et_2O was added. After 1 h, 2 M aqueous NaOH (0.5 mL) was added under a nitrogen system and the solution filtered. The filtrate was concentrated to afford our desired product (3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl)hexane-3-thiol (0.37 g, 92%) **11a** as a colorless oil; $[\alpha]_D^{25} = +13.7$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 [d, $J = 6.4$ Hz, 3H, NCHCH(CH_3)$_2$], 0.92–1.06 [m, 3H, NCHCH(CH_3)$_2$], 0.92–1.06 [m, 6H, SHCHCH(CH_3)$_2$], 1.62–1.72 [m, 4H, (CH_2)$_2$], 1.89–1.95 [m, 1H, NCHC*H*(CH_3)$_2$], 2.13–2.25 (m, 1H, SHCC*H*Me$_2$), 2.52 (dd, $J = 4.4$, 8.0 Hz, 1H, NC*H*), 2.64–2.73 (m, 4H, NCH_2), 2.92 (dd, $J = 4.4$, 7.6 Hz, 1H, C*H*S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.63, 19.57, 21.57, 21.79, 24.14, 29.40, 29.69, 48.78, 50.03, 66.20.

4.5. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)butan-1-ol 9b

$[\alpha]_D^{25} = -41.3$ (*c* 1.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, $J = 6.8$ Hz, 3H, CCH_3), 0.96 (d, $J = 6.8$ Hz, 3H, CCH_3), 1.62–1.70 [m, 4H, (CH_2)$_2$], 1.72–1.82 [m, 1H, C*H*(CH_3)$_2$], 2.54 (dd, $J = 4.4$, 8.0 Hz, 1H, NC*H*), 2.57–2.64 (m, 2H, NCH_2), 2.68–2.74 (m, 2H, NCH_2), 4.92 (d, $J = 4.0$ Hz, 1H, C*H*O), 7.14–7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.28, 21.81, 23.78, 27.88, 51.47, 72.29, 72.51, 126.08, 126.62, 127.79, 142.88 (Ph).

4.6. *S*-(1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)-butyl ethanethioate 10b

$[\alpha]_D^{25} = -240.8$ (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 0.90 (d, $J = 6.8$ Hz, 3H, CCH_3), 0.99 (d, $J = 6.4$ Hz, 3H, CCH_3), 1.45–1.55 [m, 4H, (CH_2)$_2$], 1.92–2.04 [m, 1H, C*H*(CH_3)$_2$], 2.26 (s, 3H, SCOCH_3), 2.60–2.69 (m, 4H, NCH_2), 2.97 (t, $J = 6.4$ Hz, 1H, NC*H*), 4.99 (d, $J = 6.4$ Hz, 1H, SC*H*), 7.14–7.41 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.82, 21.62, 24.31, 30.57, 30.59, 49.69, 50.42, 69.33, 126.73, 127.86, 128.70, 141.80, 194.60.

4.7. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)-butane-1-thiol 11b

$[\alpha]_D^{25} = -489.0$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, $J = 7.2$ Hz, 3H, CHCH_3), 0.99 (d, $J = 6.4$ Hz, 3H, CCH_3), 1.37–1.48 [m, 4H, (CH_2)$_2$], 2.06–2.15 [m, 1H, C*H*(CH_3)$_2$], 2.54–2.70 (m, 4H, NCH_2), 3.00 (dd, $J = 5.2$, 7.6 Hz, 1H, NC*H*), 4.30 (d, $J = 7.6$ Hz, 1H, SC*H*), 7.12–7.40 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.95, 21.67, 24.46, 30.42, 50.60, 70.03, 77.20, 126.73, 127.9, 128.1, 144.57 (Ph).

4.8. (1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethanol 9c

$[\alpha]_D^{25} = -87.5$ (*c* 1.00, $CHCl_3$); mp 114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82–1.85 [m, 4H, NCH$_2$(CH_2)$_2$], 2.59–2.62 (m, 2H, NCH_2), 2.74–2.76 (m, 2H, NCH_2), 3.30 (d, $J = 3.2$ Hz, 1H, NC*H*), 5.24 (d, $J = 3.0$ Hz, 1H, C*H*OH), 6.97–7.25 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.47, 52.94, 73.99, 77.31, 126.08, 126.70, 127.02, 127.19, 127.42, 129.25, 137.47, 140.69 (2Ph).

4.9. *S*-(1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethyl ethanethioate 10c

$[\alpha]_D^{25} = -32.5$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.78 [m, 4H, $NCH_2(CH_2)_2$], 2.28 (s, 3H, $COCH_3$), 2.50–2.57 [m, 4H, $N(CH_2)_2$], 3.48 (d, $J = 4.8$ Hz, 1H, NC*H*), 5.25 (d, $J = 5.2$ Hz, 1H, SCH), 6.88–7.26 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.33, 30.83, 52.62, 52.85, 74.99, 126.88, 127.48, 127.59, 128.88, 129.00, 138.64, 140.33.

4.10. (1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethanethiol 11c

$[\alpha]_D^{25} = -162.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72–1.79 [m, 4H, $NCH_2(CH_2)_2$], 2.29 (s, 1H, S*H*), 2.45–2.51 [m, 2H, NCH_2), 2.55–2.61 (m, 2H, NCH_2], 3.46 (d, $J = 5.6$ Hz, 1H, NC*H*), 4.70 (d, $J = 5.2$ Hz, 1H, C*H*S), 6.96–7.36 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.47, 48.60, 52.30, 75.70, 127.05, 127.09, 127.35, 127.72, 128.63, 129.79, 137.40, 140.85.

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