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New β-amino thiols as efficient catalysts for highly enantioselective alkenylzinc addition to aldehydes

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Abstract—A series of new optically active β-amino thiols and thiolacetates prepared from the simple natural amino acid, (*S*)-(−)-valine, were found to be effective catalysts for the enantioselective addition of alkenylzinc to aldehydes and thereby providing an efficient route for chiral (*E*)-allylic alcohols with ees of up to >99% in the presence of **7a** (1 mol %).

1. Introduction

Over the past two decades, great progress has been realized in the catalytic asymmetric alkyl addition to aldehydes for the generation of enantiomerically pure secondary alcohols with very high enantiomeric excess.[1] However, the enantioselective alkenyl addition to aldehydes still remains a challenge as indicated by only a few reports in the literature. The importance of alkenyl addition of aldehydes could be well understood as enantiopure allyl alcohols are enormously useful key intermediates for synthesizing a wide variety of natural products and biologically active compounds.[2] Recently Pu and Yu reviewed the results of organozinc additions to carbonyl compounds using approximately 600 individual catalysts during the last decade or so.[1a] Amino alcohols have been the choice invariably for the ligand design of many asymmetric catalytic reactions due to their excellent enantioselectivity obtainable, especially in the organozinc addition to the carbonyl compounds.

In the pioneering work of Oppolzer and Radinov,[2a] the reaction of terminal alkynes with dicyclohexylborane followed by boron–zinc exchange in the presence of β-amino alcohol, 3-*exo*-dimethylaminoisobornenol (DAIB, Noyori's ligand), as a chiral ligand was employed either in the case of intermolecular[2a] or intramolecular[2b] alkenylation of aromatic and aliphatic aldehydes with high enantioselectivities. Dahmen and Bräse also demonstrated a paracyclophane based ketimine ligand with excellent performance for enantioselective alkenylation of R-branched aliphatic aldehydes.[3] However, β-amino thiols are relatively much less explored as ligands for similar types of reactions.[4] On the other hand Wipf et al.[5] reported a method for hydrozirconation of alkynes with Cp_2ZrHCl (Schwartz reagent) then through in situ transmetalation of alkenylzirconocenes to give alkenylzinc reagents; however a relatively high catalyst loading is required in this case.

Chan et al. reported a new one-step procedure for the synthesis of optically active tertiary amino naphthol with high purity in the alkenylation of aldehydes but at 15 mol % of ligand to substrate.[6] In the reaction pathway, a zinc-based chiral Lewis acid-amino alcohol complex was first formed as an intermediate, which then adds to the aldehyde to afford the alkenylated product. While moderate to excellent stereoselectivities were achieved in the enantioselective alkenylation, the catalytic loading demands a bigger L/S ratio, which make it less attractive.

During our ongoing research, we understood that amino thiol structures serve as better alternative to amino alcohols in asymmetric alkenylzinc additions to aldehydes. Herein, we report the ability of new chiral β-amino thiol based catalytic systems for the highly effective enantioselective alkenylation with higher yields over conventional systems. It is also important to note that the L/S ratio has been reduced drastically to as low as 0.5 mol % with

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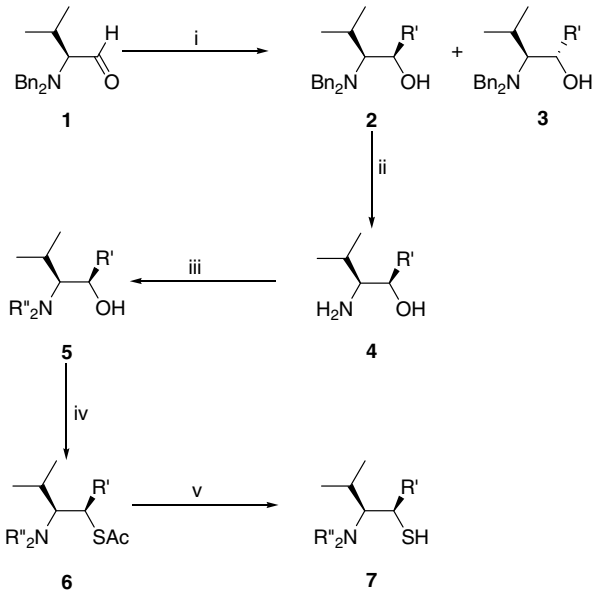
a still very high enantioselectivity. The softness of the sulfur atom in the thiol functional group invigorates the chelation effect with the zinc better than to the oxygen atom of the amino alcohol. To the best of our knowledge this is the first report on the usage of β-amino thiol ligands for the asymmetric alkenylzinc addition to aldehydes.

2. Synthesis of the chiral ligands

A typical synthetic sequence for the preparation of these chiral amino thiols is illustrated below in Scheme 1. Adopting the method of Reetz et al.,[7] *N*,*N*-dialkylation of (*S*)-(−)-valine was initially carried out 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 Swern oxidation of the *N*,*N*-dibenzylamino alcohols, alkylmagnesium bromide was added to the corresponding aldehydes **1** to give the amino alcohols **2** in high diastereoselectivity. Figure 1 shows the X-ray structure of **2′**. The protecting benzyl group was cleaved by hydrogenolysis using either Pd/C or $Pd(OH)_2$ under hydrogen (1 atm). The dialkylation of the nitrogen in **4** was then carried out with various alkyl dihalides [bis(2-bromoethyl) ether, 1,5-dibromopentane and 1,4-dibromobutane] to produce tertiary amino alcohol **5**. The hydroxyl group in **5** was transformed into the mesylate for further in situ intramolecular nucleophilic attack by the neighboring tertiary nitrogen atom thus furnishing the aziridinium ion as an intermediate with



Scheme 1. Reagents and conditions: (i) R′MgX, THF, 0 °C, 1 h; (when R′ = *i*Pr; **2**/**3** = 96/4, yield = 56%), (when R′ = Ph; **2′**/**3′** = 91/9, yield = 69%). Diastereomeric ratio was determined by ^{1}H NMR (400 MHz, Varian Mercury 400) spectroscopy; (ii) H_2, Pd/C, MeOH, 1 atm, rt, 8 h, 92%; (iii) R″Br, 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%. (1*R*,2*S*)-1,2-Diphenyl-2-amino-1-ethanol is commercially available.

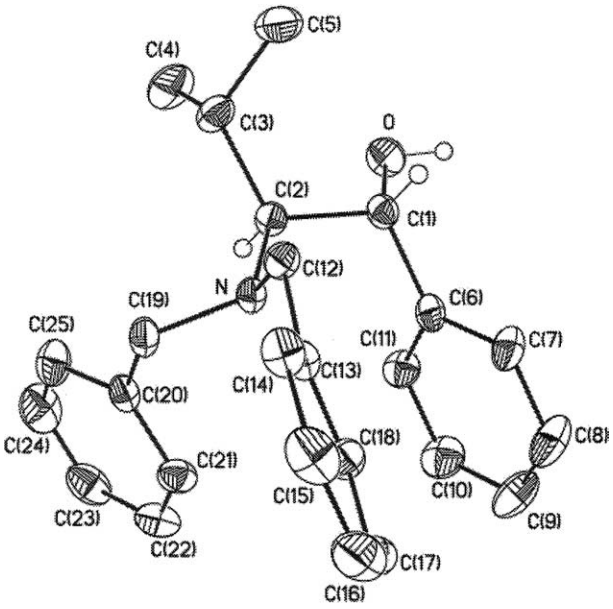


Figure 1. X-ray structure of **2′** (R′ = Ph).

an inversion of configuration.[8] This aziridium ion then undergoes regiospecific ring-opening at the benzylic position via a thiolacetate to produce the amino thiolacetate **6** with an inversion of configuration. Figure 2 shows the X-ray structure of **6h**. Then the thiolacetate group was reduced to the amino thiol **7** and the whole process carried out in a highly stereocontrolled fashion.

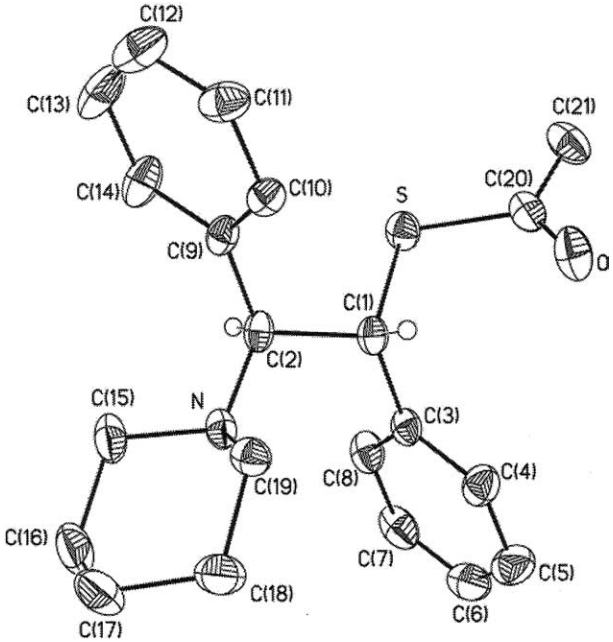


Figure 2. X-ray structure of **6h** (R′ = Ph, R''_2 = –$(CH_2)_5$–).

3. Results and discussion

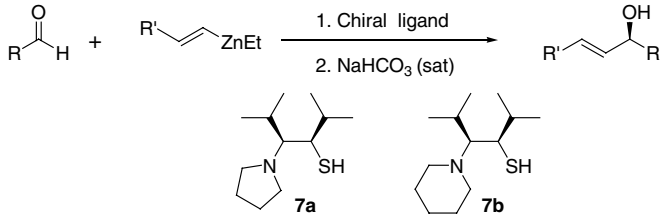
According to the protocol of Oppolzer and Radinov, the terminal alkyne was hydroborated with freshly prepared dicyclohexylborane to produce (*E*)-1-alkenylborane,

which was then treated with diethylzinc to generate alkenylzinc reagents.[2a] As suggested by Dahmen and Bräse, we employed toluene as the solvent for hydroboration to improve the solubility of substrates.[3] In general, we used 1.5 equiv of alkenylzinc reagent relative to the aldehyde in the presence of 2 mol % of ligands and the desired chiral allylic alcohols were obtained in good yields with high stereoselectivity. In agreement with Bräse's report, we found that 2 equiv of diethyl zinc and 1.5 equiv of dicyclohexylborane were essential to ensure good chemical conversion during the addition. Otherwise, the aldehyde would not be completely consumed as against the original Oppolzer's stoichiometry. The results of asymmetric alkenyl addition to various aldehydes in the presence of chiral amino thiol ligands **7a** and **7b** are summarized in Table 1.

In general, we obtained good chemical conversion and much higher enantioselectivity with the amino thiol ligands in comparison with the corresponding amino alcohol ligands. In the stoichiometric study of **7a** we found that from 5 to 0.5 mol % catalyst loading only 1.1% ee variation (entries 1–5), and the temperature effect was significant as lowering the reaction temperature from −10 to −20 °C resulted in an increase of 7% ee (entry 16 vs 17). However, further lowering reaction temperature to −40 °C did not have any influence on optical selectivity (entries 17, 18, and 19). In contrast to Dahmen and Bräse's ligands,[3] we observed that amino thiol catalyzed reactions afforded highly enantiomerically enriched products from aromatic aldehydes rather than aliphatic aldehydes. It was also found that aromatics substituted with electron withdrawing group resulted in slightly lower selectivities than those of electron rich aromatics (entries 9, 12, and 13). For the aliphatic aldehydes, the aliphatic chain on the alkyne when elongated from butyl to hexyl resulted in the highest enantioselectivity (entry 18 vs 11), while a bulky substitution on the alkyne did not have any influence (entry 4 vs 6).[9]

In Table 2, we made a parallel comparison of the competency between amino alcohols **5** and amino thiols **7** as the chiral ligands for asymmetric alkenylation of aldehydes. According to the HSAB rule, due the sulfur atom in the amino thiols being soft base, it prefers to associate strongly to the soft zinc metal than the oxygen atom of the amino alcohols. Therefore, a more stable transition state of the addition complex from the amino thiol relative to the amino alcohols would be expected. Thus, amino thiols showed much higher enantioselectivities than the corresponding amino alcohols in these asymmetric alkenyl addition processes under similar conditions. We also found that the size increment of R′ in thiols improved the enantioselectivity from phenyl to isopropyl group, which probably due to more steric congested transition state (entry 7–9 vs 16–18) (Fig. 3).

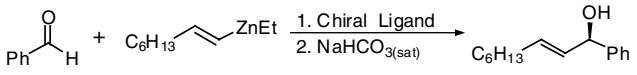
Table 1. Asymmetric alkenyl addition to aldehydes



Entry	R aldehyde	R′	Ligand	Mol % of ligand	Solvent	Temp (°C)	Yield (%)	Ee (%)[a]
1	Ph	$CH_3(CH_2)_5$	7a	0.1	Toluene	–30	62	59.4(*R*)
2	Ph	$CH_3(CH_2)_5$	7a	0.5	Toluene	–30	69	98.4(*R*)
3	Ph	$CH_3(CH_2)_5$	7a	1	Toluene	–30	80	99.1(*R*)
4	Ph	$CH_3(CH_2)_5$	7a	2	Toluene	–30	88	99.5(*R*)
5	Ph	$CH_3(CH_2)_5$	7a	5	Toluene	–30	90	99.5(*R*)
6	Ph	*tert*-Bu	7a	2	Toluene	–30	86	99.0(*R*)
7	Cyclohexyl	Ph	7a	2	Toluene	–30	72	66.5(*S*)
8	(*E*)-PhCH=CH	$CH_3(CH_2)_5$	7a	2	Toluene	–30	81	69.8(*R*)
9	Ph	$CH_3(CH_2)_5$	7b	2	Toluene	–30	84	99.0(*R*)
10	Ph	$CH_3(CH_2)_5$	7b	2	Hexane	–30	80	99.0(*R*)
11	Ph	$CH_3(CH_2)_5$	7b	5	Toluene	–30	94	99.4(*R*)
12	4-MeO-Ph	$CH_3(CH_2)_5$	7b	2	Toluene	–30	90	98.1(*R*)
13	2-Cl-Ph	$CH_3(CH_2)_5$	7b	2	Toluene	–30	86	92.6(*R*)
14	Ph	$CH_3(CH_2)_3$	7b	1	Toluene	–30	90	94.3(*R*)
15	Ph	$CH_3(CH_2)_3$	7b	2	Toluene	–30	92	94.5(*R*)
16	Ph	$CH_3(CH_2)_3$	7b	5	Toluene	–10	89	91.3(*R*)
17	Ph	$CH_3(CH_2)_3$	7b	5	Toluene	–20	94	98.3(*R*)
18	Ph	$CH_3(CH_2)_3$	7b	5	Toluene	–30	94	98.2(*R*)
19	Ph	$CH_3(CH_2)_3$	7b	5	Toluene	–40	94	98.3(*R*)
20	Ph	$CH_3(CH_2)_3$	7b	15	Toluene	–30	94	99.5(*R*)
21	2-Cl-Ph	$CH_3(CH_2)_3$	7b	5	Toluene	–30	90	98.1(*R*)

[a] Determined by HPLC (Chiracel OD-H column, flow rate : 0.7 ml/min, hexane : IPA = 97:3).

Table 2. Alkenylation to benzaldehyde with various chiral ligands



Entry	Ligand	Yield (%)	Ee (%)
1	5a	55	51.1(*R*)
2	5b	86	74.6(*R*)
3	5c	63	71.8(*R*)
4	6a	86	92.3(*R*)
5	6b	60	78.8(*R*)
6	6c	63	81.6(*R*)
7	7a	88	99.5(*R*)
8	7b	84	99.0(*R*)
9	7c	88	99.3(*R*)
10	5d	48	21.7(*R*)
11	5e	55	46.5(*R*)
12	5f	50	30.7(*R*)
13	6d	86	93.3(*R*)
14	6e	55	15.8(*R*)
15	6f	77	53.3(*R*)
16	7d	89	95.1(*R*)
17	7e	92	98.6(*R*)
18	7f	88	98.4(*R*)
19	5g	65	86.7(*R*)
20	5h	55	58.9(*R*)
21	5i	53	78.7(*R*)
22	6g	83	96.5(*R*)
23	6h	77	93.2(*R*)
24	6i	85	96.8(*R*)
25	7g	82	98.1(*R*)
26	7h	93	98.4(*R*)
27	7i	83	97.3(*R*)

All reactions are carried out with 1.5 equiv organozinc in the presence of 2 mol % chiral ligand at −30 °C and enantiomeric excess determined by HPLC (Chiracel OD-H column, flow rate: 0.7 mL/min, hexane/IPA = 97:3, retention time: 10–11 min (*R*), 14–15 min (*S*) and detected by UV irradiation at $\lambda = 254$ nm).

4. Conclusion

In summary, we have developed a new class of efficient amino thiol ligands for asymmetric alkenyl addition to aldehydes affording enantioselectivity as high as 99.1% ee with very low catalytic loading of 1 mol % (Table 1, entry 3). Further understanding of the hard–soft concept of these ligands and extended utilization of these thiols as ligands in preference to alcohols is currently underway.

5. Experimental

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed in flame-dried apparatus under an atmosphere of nitrogen at room temperature unless otherwise stated. All reactions were conducted under a nitrogen atmosphere. All chemicals and solvents were used as received unless otherwise stated. THF (Na, benzophenone), CH_2Cl_2 (CaH_2), methanol (Mg), and toluene (Na) were distilled from the drying agents indicated. Flash chromatography was carried out using Merck silica gel 60, 70–230 mesh ASTM. Melting points are uncorrected. Optical rotations were measured on PERKIN ELMER 241 polarimeter. Infrared spectra were recorded on HITACHI 270-30 Infrared Spectrophotometer. NMR spectra were recorded on Varian Mercury 400 or Varian INOVA 600. The chemical shift are reported as δ value in parts per million relative to TMS ($\delta = 0$) was used as internal standard in $CDCl_3$ for ^1H NMR spectra and the center peak of $CDCl_3$ ($\delta = 77.0$ ppm) was used as internal standard in ^{13}C NMR spectra. FAB-mass spectra were collected on JMS-700 double focusing Mass Spectrometer. Elemental analyses were collected on Foss Heraeus CHN-O-RAPID Elemental Analyzer.

5.1. (3*R*,4*S*)-4-(Dibenzylamino)-2,5-dimethylhexan-3-ol, 2

To a vigorously stirred solution of **1** (10.4 g, 35 mmol) in 35 mL THF at 0 °C by an ice bath, to the resulting solution was added 35 mL of isopropyl magnesium chloride (2.0 M, in THF) stirred for 1 h and then warmed to room temperature and quenched with NH_4Cl (aq). The aqueous solution was extracted with ethyl acetate (3×200 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude product, which was purified through column chromatography on silica gel to afford **2** (6.1 g, 56%) as a colorless oil; $[\alpha]_D^{25} = -20.4$ (*c* 5.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, $J = 7.2$ Hz, 3H, CH_3), 0.86 (d, $J = 6.8$ Hz, 3H, CH_3), 1.02 (d, $J = 7.2$ Hz, 3H, CH_3), 1.12 (d, $J = 6.8$ Hz, 3H, CH_3), 2.12–2.00 (m, 1H, $CHCN$), 2.34–2.20 (m, 1H, $CHCO$), 2.38 (dd, $J = 5.2$, 5.2 Hz, CHN), 3.54 (d, $J = 13.6$ Hz, CH_2Ph), 3.70 (s, 1H, CHO), 3.75 (d, $J = 13.6$ Hz, CH_2Ph), 7.07–7.25 (m, 10H, Ar*H*); ^{13}C

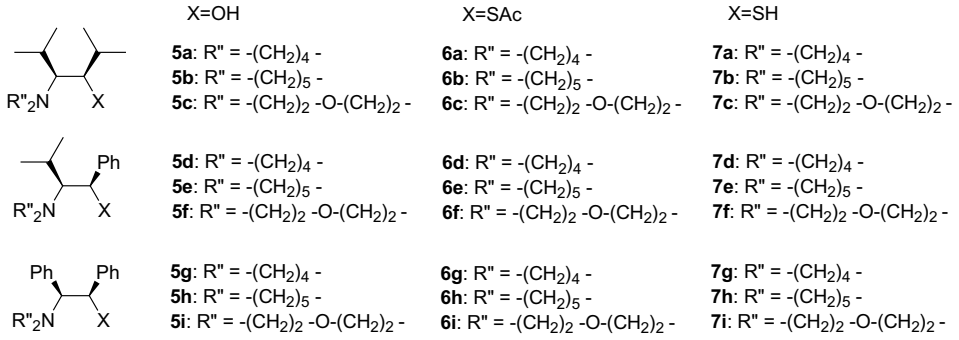


Figure 3.

NMR (100 MHz, $CDCl_3$) δ 16.93, 20.46, 20.52, 23.17, 25.87, 31.11, 54.57, 63.03, 75.33, 126.73, 128.05, 129.11, 140.29. IR (neat) 3606, 3505, 3061, 3028, 2958, 2872, 2799, 1492, 1455, 1380 cm^{-1}.

5.1.1. (1*R*,2*S*)-2-(Dibenzylamino)-3-methyl-1-phenylbutan-1-ol, 2′. To a vigorously stirred solution of **1** (10.4 g, 35 mmol) in 35 ml THF at 0 °C by ice bath, then the resulting solution was added 35 ml of phenyl magnesium chloride (2.0 M, in THF) stirred for 1 h then warmed to room temperature and quenched with $NH_4Cl_{(aq)}$. The aqueous solution extracted with ethyl acetate (3×200 ml), dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was purified through column chromatography on silica gel to afford **2′** (8.7 g, 69%) as a colorless solid; δ 0.93 (d, $J = 6.4$ Hz, 3H, CH_3), 1.18 (d, $J = 6.4$ Hz, 3H, CH_3), 2.12 (d, $J = 5.2$ Hz, 1H, CHMe$_2$), 2.23–2.40 (m, 1H, CHNBn$_2$), 2.78 (br, 1H, OH), 3.52 (d, 13.6 Hz, 2H, PhCH_2), 3.90 (d, $J = 13.6$ Hz, 2H, PhCH_2), 5.12 (s, 1H, CHO), 7.20–7.40 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.81, 22.77, 26.38, 54.99, 67.53, 71.58, 126.21, 126.84, 127.99, 128.14, 128.54, 128.95, 139.94, 144.67; HRMS(FAB): *m*/*z* calcd for $C_{25}H_{30}NO$ MH^+: 360.2328; Found : 360.2325.

X-ray crystal data for **2′**: $C_{25}H_{29}NO$, MW = 359.49, orthorhombic, space group $P2_12_12_1$, $a = 9.7113(14)$, $b = 10.4909(15)$, $c = 21.444(3)$ Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 2184.8(5)$ Å^3, $T = 293$ K, $Z = 4$, $D_c = 1.093$ g cm^{-1}, $\mu = 0.065$ mm^{-1}, $\lambda = 0.71073$ Å, $F(000)$ 776, crystal size $0.22 \times 0.46 \times 0.47$ mm^3, 3857 independent reflections ($R_{int} = 0.0506$), 11,563 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on $F^2 = 0.788$; final R indices [$I > 2\sigma(I)$] $R_1 = 0.0450$, $wR_2 = 0.1142$, SADABS.

5.2. (3*R*,4*S*)-4-Amino-2,5-dimethylhexan-3-ol, 4

To a solution of **2** (6 g, 18.5 mmol) in 100 mL of MeOH, the resulting solution was added 2 g of 10% Pd/C. The resulting solution under an H_2 balloon (1 atm) was stirred for 8 h at room temperature. Then resulting solution was filtered through celite and concentrated in vacuo to give **4** (2.5 g, 92%) as white solid; mp = 87–88 °C; $[\alpha]_D^{22} = +6.8$ (*c* 2.8, EtOH) {lit.[10] $[\alpha]_D^{25} = +7.07$ (*c* 2.05, EtOH)}; ^1H NMR (400 MHz, acetone-*d*) δ 0.92 (d, $J = 7.2$ Hz, 3H, CH_3), 0.94 (d, $J = 7.2$ Hz, 3H, CH_3), 1.03 (d, $J = 5.2$ Hz, 3H, CH_3), 1.05 (d, $J = 4.0$ Hz, 3H, CH_3), 1.90–2.04 (m, 1H, CHMe$_2$), 2.12–2.24 (m, 1H, CHMe$_2$), 2.63 (dd, $J = 8.4$, 3.2 Hz, 1H, NCH), 3.28 (dd, $J = 8.4$, 4.0 Hz, 1H, OCH), 3.37 (dd, $J = 3.0$, 1.6 Hz, 1H, COH), 4.9 (s, 2H, NH_2); ^{13}C NMR (100 MHz, acetone-*d*) δ 19.15, 21.55, 22.13, 28.00, 29.20, 67.54, 83.30; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.4$ Hz, 3H, CH_3), 0.90 (d, $J = 6.4$ Hz, 3H, CH_3), 0.94 (d, $J = 6.8$ Hz, 3H, CH_3), 0.95 (d, $J = 6.8$ Hz, 3H, CH_3), 1.90–2.04 (m, 1H, CHMe$_2$), 1.86–2.06 (m, 2H, 2CHMe$_2$), 2.59 (dd, $J = 6.8$, 4.0 Hz, 1H, CHN), 3.27 (dd, $J = 6.8$, 4.0 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.07, 16.10, 20.27, 20.86, 28.37, 29.09, 57.98, 77.18.

5.3. (3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexan-3-ol, 5a

To a mixture of **4** (5 mmol, 0.75 g) and potassium carbonate (10 mmol, 1.4 g) in 40 mL of acetonitrile was added 1,4-dibromobutane (6 mmol, 1.3 g) and then the solution heated to reflux for 18 h, after which TLC analysis of the reaction mixture indicated the completion of the reaction. The resulting solution was filtered and the acetonitrile evaporated, at which point water (30 mL) was added, then extracted with ethyl acetate (3×30 mL). 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 **5a** (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, NCHCHCH_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, NCCH(CH$_3$)$_2$), 2.05–2.12 (m, 1H, OCCH(CH$_3$)$_2$), 2.21 (dd, $J = 3.2$, 4.4 Hz, 1H, NCH), 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, CHO); ^{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; HRMS (FAB): *m*/*z* calcd for $C_{12}H_{25}NO$ MH^+: 200.2014; found: 200.2011; IR (neat) 3391, 2960, 2873, 2802, 1677, 1598, 1515, 1464 cm^{-1}; Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.28; H, 12.73; N, 6.99.

5.4. (*S*)-(3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexan-3-yl ethanethioate, 6a

To a vigorously stirred solution of **5a** (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 which TLC analysis of the reaction mixture indicated the completion of reaction; CH_2Cl_2 was then removed in vacuum. To the residue was added benzene (30 mL), 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 the solvent, the residued oil was purified through column chromatography (eluent: *n*-hexane/NEt_3 = 100:1) on silica gel to afford **6a** (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)$_2$), 0.94 (d, $J = 6.8$ Hz, 3H, NCHCH-(CH_3)$_2$), 0.95 (d, $J = 6.4$ Hz, 3H, SCHCH(CH_3)$_2$), 0.96 (d, $J = 6.4$ Hz, 3H, SCHCH(CH_3)$_2$), 1.66–1.71 (m, 4H, CCH_2), 1.88–2.00 (m, 1H, NCCH(CH$_3$)), 2.01–2.12 (m, 1H, SCCHMe$_2$), 2.34 (s, 3H, SCO*Me*), 2.62–2.70 (m, 2H, NCH_2), 2.68 (dd, $J = 5.6$, 6.4 Hz, 1H, NCH), 2.71–2.77 (m, 2H, NCH_2), 3.79 (dd, $J = 5.2$, 6.4 Hz, 1H, CHS); ^{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; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{27}NOS$ MH^+: 258.1891; found: 258.1899; Anal. Calcd for $C_{14}H_{27}NOS$: C, 65.32; H, 10.57; N, 5.44. Found: C, 65.38; H, 10.60; N, 5.41.

5.5. (3*R*,4*S*)-2,5-Dimethyl-4-(pyrrolidin-1-yl)hexane-3-thiol, 7a

To a suspension solution of LAH (4 mmol, 0.16 g) in 10 mL of dry Et_2O in an ice bath, a solution of (*S*)-(3*R*,4*S*)-2,5-dimethyl-4-(pyrrolidin-1-yl)hexan-3-yl ethanethioate **6a** (2 mmol, 0.52 g) in 20 mL of dry Et_2O was added. After 1 h 2M aqueous NaOH (0.5 mL) was added under nitrogen 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%) **7a** as a colorless oil; $[\alpha]_D^{25} = +13.7$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.4$ Hz, 3H, NCHCH(CH_3)$_2$), 0.93 (d, $J = 4.0$ Hz, 3H, SCHCH(CH_3)$_2$), 0.94 (d, $J = 6.4$ Hz, 3H, NHCHCH(CH_3)$_2$), 0.96 (d, $J = 4.0$ Hz, 3H, SCHCH(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, SCC*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; HRMS (FAB): *m*/*z* calcd for $C_{12}H_{25}NS$ MH^+: 216.1786; found: 216.1742.

5.6. (3*R*,4*S*)-2,5-Dimethyl-4-(piperidin-1-yl)hexan-3-ol, 5b

To a mixture of (3*R*,4*S*)-4-amino-2,5-dimethylhexan-3-ol **4** (5 mmol, 0.75 g) and potassium carbonate (10 mmol, 1.4 g) in 40 mL of acetonitrile was added 1,5-dibromopentane (6 mmol, 1.39 g); the solution was then heated to reflux for 18 h, after which TLC analysis of the reaction mixture indicated the completion of the reaction. The resulting solution was filtered and the acetonitrile evaporated. After removal of acetonitrile, water (30 mL) was added and 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 **5b** (0.95 g, 89%) as a white solid; mp 46 °C; $[\alpha]_D^{22} = -7.4$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, $J = 6.8$ Hz, 3H, CH_3), 0.93 (d, $J = 6.8$ Hz, 3H, CH_3), 0.95 (d, $J = 6.8$ Hz, 3H, CH_3), 0.99 (d, $J = 6.8$ Hz, 3H, CH_3), 1.37–1.42 (m, 2H, (CH$_2$)$_2$CH_2(CH$_2$)$_2$), 1.42–1.52 (m, 4H, N(CH$_2$CH_2)$_2$), 1.85–1.88 (m, 1H, C*H*Me$_2$), 1.90–2.10 (m, 1H, C*H*Me$_2$), 2.14 (dd, $J = 4.8$, 4.4 Hz, 1H, NC*H*), 2.47–2.59 (m, 4H, NCH_2), 3.49 (dd, $J = 5.2$, 4.8 Hz, 1H, *H*CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.42, 20.69, 20.86, 22.50, 24.95, 26.85, 27.00, 30.10, 51.73, 72.19, 74.52; IR (neat) 3492, 2931, 2873, 2974, 2741, 1465,1384 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{13}H_{27}NO$ MH^+: 214.2171; found: 214.2170; Anal. Calcd for $C_{13}H_{27}NO$: C, 73.18; H, 12.76; N, 7.50. Found: C, 73.16; H, 12.77; N, 7.49.

5.7. (*S*)-(3*R*,4*S*)-2,5-Dimethyl-4-(piperidin-1-yl)hexan-3-yl ethanethioate, 6b

According to the general procedure, **5b** (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 followed by MsCl (8 mmol, 0.62 mL). The resulting solution was stirred for 1 h at 0 °C, after which TLC analysis of the reaction mixture indicated the completion of reaction; CH_2Cl_2 was then removed in vacuum. Benzene (30 mL) and NEt_3 (12 mmol, 1.8 mL) and thioacetic acid (8 mmol, 0.57 mL) were added to the residue, then heated to reflux for 8 h and 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 **6b** (0.75 g, 69%) as a colorless oil; $[\alpha]_D^{25} = -8.85$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, $J = 6.4$ Hz, 3H, CH_3), 0.89 (d, $J = 2.8$ Hz, 3H, CH_3), 0.90 (d, $J = 2.8$ Hz, 3H, CH_3), 0.91 (d, $J = 6.4$ Hz, 3H, CH_3), 1.34–1.50 (m, 6H, (CH$_2$)$_2$CH_2(CH_2)$_2$), 1.97–2.12 (m, 1H, C*H*Me$_2$), 2.30 (s, 3H, COCH_3), 2.39 (dd, $J = 6.8$, 5.0 Hz, 1H, NC*H*), 2.42–2.67 (m, 4H, NCH_2), 3.79 (dd, $J = 6.8$, 5.2 Hz, 1H, C*H*SAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.13, 20.75, 20.94, 21.20, 24.96, 26.86, 29.62, 30.71, 30.76, 49.00, 50.89, 70.09, 195.31; IR (neat) 2929, 2869, 2393, 2241, 1691 cm^{-1}; Anal. Calcd for $C_{15}H_{29}NOS$: C, 66.37; H, 10.77; N, 5.16. Found: C, 66.35; H, 10.79; N, 5.18; MS (FAB) 272 (MH^+) (100%), 228, 196, 154 (100%); HRMS (FAB): *m*/*z* calcd for $C_{15}H_{29}NOS$ MH^+: 272.2048; found: 272.2039.

5.8. (3*R*,4*S*)-2,5-Dimethyl-4-(piperidin-1-yl)hexane-3-thiol, 7b

According to the reduced procedure, **7b** (0.39 g, 90%) was obtained as a colorless oil; $[\alpha]_D^{25} = -136$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, $J = 6.8$ Hz, 3H, CH_3), 0.94 (d, $J = 6.8$ Hz, 3H, CH_3), 0.97 (d, $J = 2.8$ Hz, 3H, CH_3), 0.91 (d, $J = 6.4$ Hz, 3H, CH_3), 1.36–1.42 (m, 2H, CH_2), 1.44–1.48 (m, 4H, CH$_2$(CH_2)$_2$), 2.09–2.13 (m, 1H, C*H*Me$_2$), 2.18–2.24 (m, 1H, C*H*Me$_2$) 2.50–2.60 (m, 4H, NCH_2), 2.22–2.30 (dd, $J = 4.0$, 3.6 Hz 1H, NC*H*), 2.93 (dd, $J = 4.8$, 4.0 Hz 1H, C*H*S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.48, 20.75, 21.88, 25.07, 26.95, 28.81, 29.67, 47.58, 51.56, 72.16; Anal. Calcd for $C_{13}H_{27}NS$: C, 68.06; H, 11.86; N, 6.11. Found: C, 68.01; H, 11.78; N, 6.07.

5.9. (3*R*,4*S*)-2,5-Dimethyl-4-morpholinohexan-3-ol, 5c

According to the *N*-alkylation procedure **5c** (84%) was obtained as a white solid; mp 56–58 °C; $[\alpha]_D^{22} = -10.5$ (*c* 2.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J = 6.8$ Hz, 3H, CH_3), 0.92 (d, $J = 6.8$ Hz, 3H, CH_3), 0.98 (d, $J = 13.6$ Hz, 3H, CH_3), 1.01 (d, $J = 13.6$ Hz, 3H, CH_3), 1.89–1.93 (m, 1H, C*H*Me$_2$), 2.04–2.09 (m, 1H, C*H*Me$_2$), 2.19 (dd, $J = 6.0$, 5.6 Hz, 1H, NC*H*), 2.52–2.65 (m, 4H, NCH_2), 3.54 (dd, $J = 5.2$, 5.0 Hz, 1H, C*H*O), 3.62 (t, $J = 9.2$ Hz, 4H, OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 16.55, 20.42, 20.73, 22.10, 26.57, 30.56, 50.64, 67.72, 71.00, 74.42; IR (neat) 3479 (OH), 2958, 2869, 2811, 1465 cm^{-1}; Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.67; H, 11.53; N, 6.57; HRMS (FAB): *m*/*z* calcd for $C_{12}H_{25}NO_2MH^+$: 216.8928; found: 216.8925.

5.10. (*S*)-(3*R*,4*S*)-2,5-Dimethyl-4-morpholinohexan-3-yl ethanethioate, 6c

According to the general procedure, to **5c** (4.0 mmol, 0.8 g) and 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 which TLC analysis of the reaction mixture indicated the completion of reaction, then CH_2Cl_2 was removed in vacuum. To the residue were added benzene (30 mL), NEt_3 (12 mmol, 1.8 mL), and thioacetic acid (8 mmol, 0.57 mL) then heated to reflux for 8 h and 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 **6c** (0.72 g, 66%) as a light red oil; $[\alpha]_D^{23} = -10.6$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.4 Hz, 3H, C*Me*), 0.90 (d, J = 4.8 Hz, 3H, C*Me*), 0.91 (d, J = 6.4 Hz, 3H, C*Me*), 0.92 (d, J = 4.8 Hz, 3H, C*Me*), 2.00–2.18 (m, 2H, C*H*Me$_2$), 2.30 (s, 3H, CO*Me*), 2.38 (dd, J = 6.4, 4.0 Hz, 1H, C*H*N), 2.50–2.2.60 (m, 2H, CH_2N), 2.65–2.2.75 (m, 2H, CH_2N), 3.60 (t, J = 4.0 Hz, OCH_2, 4H), 3.78 (dd, J = 5.6, 4.0 Hz, 1H, C*H*S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.10, 20.58, 20.86, 21.00, 29.43, 29.51, 30.54, 49.65, 50.01, 67.46, 69.68, 194.66; IR (neat) 2960, 2852, 2814, 1691, 1459, 1359, 1290 cm^{-1}; Anal. Calcd for $C_{14}H_{27}NO_2S$: C, 61.50; H, 9.95; N, 5.12. Found: C, 61.55; H, 9.90; N, 5.18; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{27}NO_2S$ MH$^+$: 274.1840; found: 274.1842.

5.11. (3*R*,4*S*)-2,5-Dimethyl-4-morpholinohexane-3-thiol, 7c

According to the reduced procedure **7c** (92%) was obtained as a colorless oil; $[\alpha]_D^{22} = -14.4$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.4 Hz, 3H, CH_3), 1.01 (d, J = 4.8 Hz, 3H, C*Me*), 1.01 (d, J = 6.4 Hz, 3H, C*Me*), 1.02 (d, J = 4.8 Hz, 3H, C*Me*), 2.07–2.20 (m, 1H, C*H*Me$_2$), 2.20–2.32 (m, 1H, C*H*Me$_2$), 2.26–2.35 (m, 1H, C*H*N), 2.58–2.73 (m, 4H, NCH_2), 2.98 (td, J = 8.0, 4.0 Hz, 1H, C*H*S), 3.62 (t, J = 4.4 Hz, 4H, CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.83, 20.68, 21.72, 21.79, 28.73, 29.66, 29.93, 47.17, 50.64, 67.67, 71.52; IR (neat) 2958, 2929, 2852, 2811, 1458, 1374, 1290 cm^{-1}; Anal. Calcd for $C_{12}H_{25}NOS$: C, 62.29; H, 10.89; N, 6.05. Found: C, 62.30; H, 10.84; N, 6.10; HRMS (FAB): *m*/*z* calcd for $C_{12}H_{25}NOS$ MH$^+$: 223.1735; found: 223.1736.

5.12. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)-butan-1-ol, 5d

According to *N*-alkylation procedure **5d** (82%) was obtained as a colorless viscous oil; $[\alpha]_D^{25} = -41.3$ (*c* 1.38, $CHCl_3$); ^{1}H 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, CH(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 = 4.4 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); IR (neat): 3425, 3027, 2958, 2874, 2803.1671, 1492 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.11; H, 9.73; N, 6.23; HRMS (FAB): *m*/*z* calcd for $C_{15}H_{23}NO$ MH$^+$: 234.1858; found: 234.1865.

5.13. (*S*)-(1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)butyl ethanethioate, 6d

According to the general procedure, **6d** (62%) was obtained as a colorless oil; $[\alpha]_D^{25} = -240.8$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CH(CH$_3$)$_2$), 2.26 (s, 3H, SCOCH_3), 2.60–2.69 (m, 4H, NCH_2), 2.97 (dd, J = 6.4, 6.0 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 (Ph), 194.60 (SCOCH$_3$); IR (neat): 2959, 1690, 1133 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{25}NOS$ MH$^+$: 292.1735; found: 292.1733.

5.14. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(pyrrolidin-1-yl)-butane-1-thiol, 7d

According to the reduced procedure, **7d** (90%) was obtained as a colorless oil; $[\alpha]_D^{25} = -489.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3H, CHCH_3), 0.99 (d, J = 6.8 Hz, 3H, CCH_3), 1.37–1.48 (m, 4H, (CH_2)$_2$), 2.06–2.15 (m, 1H, CH(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); HRMS (FAB): *m*/*z* calcd for $C_{15}H_{23}NS$ MH$^+$: 250.1629; found: 250.1633.

5.15. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(piperidin-1-yl)butan-1-ol, 5e

According to the *N*-alkylation procedure, **5e** (88%) was obtained as a colorless viscous oil; $[\alpha]_D^{25} = -21.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 3.0 Hz, 3H, CH_3), 1.08 (d, J = 3.0 Hz, 3H, CH_3), 1.36–1.45 (m, 6H, (CH_2)$_2$CH_2(CH_2)), 1.70–1.82 (m, 1H, C*H*Me$_2$), 2.35–2.45 (m, 5H, NCH_2), 4.78 (d, J = 4.4 Hz, 1H, C*H*OH), 7.15–7.42 (m, 5H, ArH); ^{13}C (100 MHz, $CDCl_3$) δ 21.95, 22.45, 24.73, 27.13, 28.02, 52.87, 70.30, 77.32, 126.12, 126.83, 127.67, 142.86 (Ph); IR (neat): 3441, 2930, 2852, 2804, 1493 cm^{-1}; Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.95; H, 10.18; N, 5.75; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{25}NO$ MH$^+$: 248.2014; found: 248.2011.

5.16. (*S*)-(1*R*,2*S*)-3-Methyl-1-phenyl-2-(piperidin-1-yl)butyl ethanethioate, 6e

According to the general procedure **6e** (62%) was obtained as a light yellow oil; $[\alpha]_D^{25} = -172.1$ (*c* 1, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) δ 0.96 (d, J = 2.0 Hz, 3H, CCH_3), 1.06 (d, J = 4.0 Hz, 3H, CHCH_3), 1.31–1.37 (m, 6H, CH_2(CH_2)$_2$), 1.98–2.03 (m, 1H, CH(CH$_3$)$_2$), 2.26 (s,

3H, SCOCH_3), 2.37–2.42 (m, 2H, NCH_2), 2.43–2.55 (m, 2H, NCH_2), 2.74 (dd, J = 6.0, 5.6 Hz, 1H, NCH), 4.98 (d, J = 6.0 Hz, 1H, SCH), 7.18–7.43 (m, 5H, ArH); ^{13}C (100 MHz, $CDCl_3$) δ 20.57, 21.79, 24.82, 26.79, 26.85, 30.18, 30.50, 49.23, 52.20, 74.69, 126.66, 127.92, 128.52, 141.987 (Ph), 194.46; IR (neat): 2930, 1690, 1447, 1380 cm^{-1}; Anal. Calcd for $C_{21}H_{25}NOS$: C, 77.77; H, 8.91; N, 4.59. Found: C, 77.75; H, 8.81; N, 4.67; MS (FAB): 306 (MH^+), 262 (M−COMe), 230 (M−SAc), 140 (100%, M−BnSAc); HRMS (FAB) m/z calcd for $C_{21}H_{25}NOS$ MH^+: 306.1891; found: 306.1889.

5.17. (1*R*,2*S*)-3-Methyl-1-phenyl-2-(piperidin-1-yl)-butane-1-thiol, 7e

According to the reduced procedure **7e** (88%) was obtained as a colorless oil; $[\alpha]_D^{25} = -83.6$ (c 1, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 3H, CH(CH_3)$_2$), 0.99 (d, J = 6.4 Hz, 3H, CH(CH_3)$_2$), 1.18–1.28 (m, 6H, C(CH_2CH_2)$_2$), 2.06–2.16 (m, 1H, CH(CH$_3$)$_2$), 2.31–2.53 (m, 4H, N(CH_2)$_2$, 2.75 (dd, J = 6.4, 6.8 Hz, 1H, NCH), 4.20 (d, J = 6.4 Hz, 1H, SCH), 7.20–7.42 (m, 5H, ArH); ^{13}C (100 MHz, $CDCl_3$) δ 19.63, 21.69, 24.87, 26.80, 26.90, 30.21, 44.43, 52.68, 75.91, 126.66, 127.87, 128.03, 144.48 (Ph); Anal. Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.57; N, 5.32. Found: C, 72.90; H, 9.51; N, 5.29; HRMS (FAB) m/z calcd for $C_{16}H_{25}NS$ MH^+: 264.1786; found: 264.1788.

5.18. (1*R*,2*S*)-3-Methyl-2-morpholino-1-phenylbutan-1-ol, 5f

According to the *N*-alkylation procedure, **5f** (86%) was obtained as a white solid; mp 90–92 °C; $[\alpha]_D^{25} = -9.16$ (c 21.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 6.4 Hz, 3H, CH_3), 1.12 (d, J = 6.4 Hz, 3H, CH_3), 1.85–2.0 (m, 1H, CHMe$_2$), 2.35–2.72 (m, 5H, CHNCH_2), 3.51–3.65 (m, 4H, CH_2OCH_2), 4.88 (d, J = 1.6 Hz, 1H, CHO), 7.21–7.41 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.34, 21.53, 27.28, 51.15, 67.46, 70.23, 76.08, 125.78, 126.59, 127.58, 143.40 (Ph); IR (neat): 3436, 2956, 2856, 2816, 1450, 1384 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.20; H, 9.25; N, 5.63; HRMS (FAB) m/z calcd for $C_{15}H_{23}NO_2MH^+$: 250.1887; found: 250.1885.

5.19. (*S*)-(1*R*,2*S*)-3-Methyl-2-morpholino-1-phenylbutyl ethanethioate, 6f

According to the general procedure, **6f** (67%) was obtained as a light yellow viscous oil; $[\alpha]_D^{22} = -187.8$ (c 1.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 6.4 Hz, 3H, CH_3), 1.00 (d, J = 6.4 Hz, 3H, CH_3), 1.82–2.0 (m, 1H, CHMe$_2$), 2.18 (s, 3H, COCH_3), 2.31–2.57 (m, 4H, CH_2NCH_2), 2.63 (dd, J = 4.8, 4.4 Hz, 1H, CHN), 3.40 (t, J = 4.4 Hz, 4H, CH_2OCH_2), 4.89 (d, J = 4.4 Hz, 1H, CHO), 7.05–7.4 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.50, 21.65, 30.42, 49.16, 51.38, 67.49, 74.15, 126.95, 127.87, 128.46, 141.08, 194.08; IR (neat): 2956, 2850, 1689, 1115 cm^{-1}; Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.43; H, 8.18; N, 4.60; MS (FAB) m/z: 306 (M^+), 264 (M−Ac), 232 (M−SAc), 142 (100%, M−Bn−SAc); HRMS (FAB) m/z calcd for $C_{17}H_{25}NO_2S$ M^+: 307.1606; found: 307.1600.

5.20. (1*R*,2*S*)-3-Methyl-2-morpholino-1-phenylbutane-1-thiol, 7f

According to reduced procedure to afford **7f** (91%) as a colorless oil; $[\alpha]_D^{25} = -80.2$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 4.0 Hz, 3H, CHCH_3), 1.13 (d, J = 4.0 Hz, 3H, CCH_3), 2.07 (d, J = 3.0 Hz, 1H, SH), 2.18–2.23 (m, 1H, CH(CH$_3$)$_2$), 2.49–2.59 (m, 4H, NCH_2CH$_2$), 2.79 (dd, J = 6.0, 5.6 Hz, 1H, NCH), 3.46–3.51 (m, 4H, CH$_2$CH_2O), 4.29 (dd, J = 6.8, 7.2 Hz, 1H, SCH), 7.21–7.42 (m, 5H, ArH); ^{13}C (100 MHz, $CDCl_3$) δ 19.69, 21.87, 30.49, 44.54, 52.10, 67.97, 75.56, 127.30, 128.23, 128.44, 128.49, 144.36 (Ph); Anal. Calcd for $C_{15}H_{23}NOS$; C, 67.88; H, 8.73; N, 5.28. Found: C, 67.95; H, 8.70; N, 5.30; MS (FAB) m/z: 265 (M^+), 232 (M−SH), 142 (100%, M−Bn−SH); HRMS (FAB) m/z calcd for $C_{15}H_{23}NOS$ MH^+: 266.1578; found: 266.1576.

5.21. (1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethanol, 5g

According to the *N*-alkylation procedure, **5g** (86%) was obtained as a white solid; mp 113–114 °C; $[\alpha]_D^{25} = -87.5$ (c 1, $CHCl_3$); ^{1}H 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, NCH), 5.24 (d, J = 3.2 Hz, 1H, CHOH), 6.97–7.25 (m, 10H, ArH); ^{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); IR (neat): 3031, 2967, 2872, 2799, 1491, 1452 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.91; N, 5.24. Found: C, 80.83; H, 7.95; N, 5.21; HRMS (FAB) m/z calcd for $C_{18}H_{21}NO$ MH^+: 268.1701; found: 268.1700.

5.22. (*S*)-(1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethyl ethanethioate, 6g

According to general procedure, **6g** was obtained as a white solid; mp 123–125 °C; $[\alpha]_D^{25} = -32.5$ (c 1.0, $CHCl_3$); ^{1}H 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, NCH), 5.25 (d, J = 5.2 Hz, 1H, SCH), 6.88–7.26 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 23.33, 30.83, 52.62, 52.85, 74.99, 126.88, 127.48, 127.59, 128.88, 129.00, 138.64, 140.33 (2Ph), 196.58; Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 73.55; H, 7.26; N, 4.38; HRMS (FAB) m/z calcd for $C_{20}H_{23}NOS$ MH^+: 326.1578; found: 326.1580.

5.23. (1*R*,2*S*)-1,2-Diphenyl-2-(pyrrolidin-1-yl)ethanethiol, 7g

According to the reduced procedure, **7g** (90%) was obtained as a colorless viscous oil; $[\alpha]_D^{25} = -162.0$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.79 (m, 4H, NCH$_2$(CH_2)$_2$), 2.29 (s, 1H, SH), 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, $CDCl_3$) 23.47, 48.60, 52.30, 75.70, 127.05, 127.09, 127.35, 127.72, 128.63, 129.79, 137.40, 140.85 (2Ph); Anal. Calcd for $C_{18}H_{21}NS$: C, 76.28; H, 7.47; N, 4.94. Found: C, 76.06; H, 7.28; N, 5.23; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{21}NS$ MH^+: 284.1473; found: 284.1477.

5.24. (1*R*,2*S*)-1,2-Diphenyl-2-(piperidin-1-yl)ethanol, 5h

According to *N*-alkylation procedure to afford **5h** (87%) was obtained as a white solid; mp 93–95 °C; $[\alpha]_D^{25} = -74.2$ (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.49 (m, 2H, $((CH_2)_2CH_2(CH_2)_2)$), 1.55–1.62 (m, 4H, $N(CH_2CH_2)_2$), 2.47–2.55 (m, 2H, NCH_2), 2.58–2.71 (m, 2H, NCH_2), 3.38 (d, J = 4.0 Hz, 1H, NC*H*), 5.38 (d, J = 4.0 Hz, 1H, C*H*O), 6.98–7.26 (m, 10H, Ar*H*); ^{13}CNMR (100 MHz, $CDCl_3$) δ 24.60, 26.28, 52.51, 71.55, 76.42, 126.14, 126.58, 127.01, 127.42, 129.43, 136.64, 141.38 (2Ph); IR (neat): 2940, 2916, 2850, 2795, 1448, 1336 cm^{-1}; HRMS (FAB)*m*/*z* calcd for $C_{19}H_{23}NO$ MH^+: 282.1858; found: 282.1857.

5.25. (*S*)-(1*R*,2*S*)-1,2-Diphenyl-2-(piperidin-1-yl)ethyl ethanethioate, 6h

According to the general procedure **6h** (62%) was obtained as a white solid; mp 112–113 °C; $[\alpha]_D^{22} = -128.4$ (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.22 (m, 2H, $((CH_2)_2CH_2(CH_2)_2)$), 1.22–1.31 (m, 2H, NCH_2CH_2), 1.31–1.40 (m, 2H, NCH_2CH_2), 2.14 (s, 3H, $COCH_3$), 2.12–2.20 (m, 2H, NCH_2), 2.38–2.50 (m, 2H, NCH_2), 3.82 (d, J = 10.4 Hz, 1H, NC*H*), 5.31 (d, J = 10.4 Hz, 1H, SC*H*), 7.10–7.31 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.42, 26.04, 30.49, 48.78, 50.71, 73.28, 126.67, 127.32, 127.59, 127.81, 128.25, 128.72, 136.03, 141.72 (2Ph); IR (neat): 2931, 1690, 1449 cm^{-1}; Anal. Calcd for $C_{21}H_{25}NOS$: C, 74.29; H, 7.42; N, 4.13; O, 4.71; S, 9.45. Found: C, 74.26; H, 7.33; N, 4.24; S, 9.61; EIMS: *m*/*z* 264 (M−SAc), 213, 174 (100%, M−BnSAc); HRMS (FAB) *m*/*z* calcd for $C_{21}H_{25}NOS$ MH^+: 340.1735; found: 340.1731.

X-ray crystal data for **6h**: $C_{21}H_{25}NOS$, MW = 339.48, trigonal, space group $P3_1$, a = 9.1843(4), b = 9.1843(4), c = 19.6583(13) Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 120°$, U = 1446.05(13) Å^3, T = 293 K, Z = 3, D_c = 1.178 g cm^{-1}, μ = 0.176 mm^{-1}, λ = 0.71073 Å, F(000) 546, crystal size 0.33 × 0.61 × 0.67 mm^3, 3729 independent reflections (R_{int} = 0.0196), 8072 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on F^2 = 0.947; final R indices [$I > 2\sigma(I)$] R_1 = 0.0371, wR_2 = 0.1130, SADABS. CCDC No. 261563.

5.26. (1*R*,2*S*)-1,2-Diphenyl-2-(piperidin-1-yl)ethanethiol, 7h

According to the reduced procedure **7h** (89%) was obtained as a viscous liquid; $[\alpha]_D^{25} = -128.4$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.39 (m, 6H, $CH_2(CH_2)_2CN$), 2.01 (br, 1H, CS*H*), 2.10–2.30 (m, 2H, CH_2N), 2.30–2.41 (m, 2H, CH_2N), 3.78 (d, J = 9.6 Hz, 1H, NC*H*), 4.68 (d, J = 9.6 Hz, 1H, SC*H*), 7.14–7.30 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.42, 26.12, 44.75, 50.86, 76.36, 126.84, 27.32, 127.61, 127.89, 128.03, 129.22, 135.75, 142.03 (2Ph); IR (neat): 3061, 3026, 2933, 2850, 2798, 1601 cm^{-1}; Anal. Calcd for $C_{19}H_{23}NS$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.67; H, 7.66; N, 4.56; MS(EI) *m*/*z*: calcd for $C_{19}H_{23}NS$ M^+: 264 (M−SH), 180, 174 (100%, M−BnSH).

5.27. (1*R*,2*S*)-2-Morpholino-1,2-diphenylethanol, 5i

According to the *N*-alkylation procedure **5i** (90%) was obtained as a white solid; mp 123–125 °C; $[\alpha]_D^{25} = -140.7$ (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50–2.60 (m, 2H, NCH_2), 2.61–2.72 (m, 2H, NCH_2), 3.30 (br, 1H, O*H*), 3.36 (d, J = 4.0 Hz, 1H, NC*H*), 3.67–3.81 (m, 4H, $O(CH_2)_2$), 5.33 (d, J = 4.0 Hz, 1H, C*H*O), 6.94–7.26 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.96, 67.11, 71.18, 76.44, 126.11, 126.87, 127.40, 127.56, 127.60, 129.54, 135.56, 140.81 (2Ph); IR (neat): 2969, 2882, 2846, 2806, 2759, 2689, 1449, 1334 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.33; H, 7.46; N,4.93. Found: C, 76.38; H, 7.36; N, 4.90; HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{21}NO_2$ MH^+: 284.1650; found: 284.1644.

5.28. (*S*)-(1*R*,2*S*)-2-Morpholino-1,2-diphenylethyl ethanethioate, 6i

According to the general procedure, **6i** (65%) was obtained as light red solid; mp 128–130 °C; $[\alpha]_D^{25} = -94.3$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, $COCH_3$), 2.31–2.38 (m, 2H, $N(CH_2)_2$), 2.41–2.51 (m, 2H, $N(CH_2)_2$), 3.44–3.58 (m, 4H, $O(CH_2)_2$), 3.72 (d, J = 8.4 Hz, 1H, NC*H*), 5.28 (d, J = 8.4 Hz, 1H, SC*H*), 7.05–7.27 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.58, 48.88, 50.49, 66.95, 73.63, 126.93, 127.72, 127.78, 127.86, 128.43, 128.94, 135.88, 140.87 (2Ph); IR (neat): 2956, 2852, 2813, 1689, 1450, 1353 cm^{-1}; Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.85; H, 6.14; N, 4.69; HRMS (FAB) *m*/*z*: calcd for $C_{20}H_{23}NO_2S$ MH^+: 342.1527; found: 342.1533.

5.29. (1*R*,2*S*)-2-Morpholino-1,2-diphenylethanethiol, 7i

According to the reduced procedure, **7i** (90%) was obtained as a viscous liquid; $[\alpha]_D^{25} = -113.7$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (br, 1H, S*H*), 2.32–2.46 (m, 4H, $N(CH_2)_2$), 3.46–3.59 (m, 4H, $O(CH_2)_2$), 3.71 (d, J = 8.4 Hz, 1H, NC*H*), 4.70 (d, J = 8.4 Hz, 1H, C*H*S), 7.12–7.30 (m, 10H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.75, 50.44, 66.95, 75.87, 127.10, 127.67, 127.94, 128.14, 129.44, 135.10, 141.24 (2Ph); HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{21}NOS$ MH^+: 300.1422; found: 300.1429.

6. Typical procedure for alkenylzinc addition to aldehydes

6.1. (*R*,*E*)-1-Phenylnon-2-en-1-ol

To a stirring solution of dicyclohexylborane (1.5 mmol) in toluene (0.5 mL) was added 1-octyne (0.26 mL,

1.5 mmol) and the mixture stirred for 1 h at room temperature, and then cooled to −78 °C. A solution of diethyl zinc (2.0 mmol, 1.1 M in toluene) was added slowly to this and after 1 h at −78 °C, a toluene solution of ligand (0.2 mL, 0.1 M in toluene, 0.02 mmol) was added. The temperature was then raised to −30 °C over a period of 0.5 h and the aldehyde (1.0 mmol) added slowly and the final mixture allowed to stir for 15 h at −30 °C. The reaction was quenched with saturated $NaHCO_3$ and the resulting mixture extracted with 3×10 mL of EtOAc, washed with brine, dried over Na_2SO_4, and solvent removed in vacuo. The residue was purified through column chromatography on silica gel to provide the enantiomerically pure allyl alcohol. HPLC (Chiracel OD-H, *n*-heptane/*i*-PrOH = 97:3): 99.5% ee (*R*) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H, CH_3), 1.23–1.43 (m, 6H), 2.00–2.08 (m, 2H, $CHCH_2CH_2$), 5.15 (d, br, J = 6.6 Hz, 1H, $PhCH(OH)CH$), 5.64 (ddt, J = 15.6, 6.6, 1.4 Hz, 1H, $CH(OH)CHCH$), 5.75 (dt, J = 15.6, 6.6 Hz, 1H, $CHCHCH_2$), 7.23–7.38 (m, 5H, HAr) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 22.47, 28.71, 29.08, 31.38, 32.11, 75.10, 125.96, 127.26, 128.25, 132.00, 132.65, 143.20 ppm; IR (neat) 2955, 2930, 2857, 1621, 1599, 1579, 1450, 1287, 1228, 697 cm^{-1}; MS (70 eV, EI), *m*/*z* (%): 218 (1) [M$^+$], 159, 145, 133, 120 (50), 105 (100), 77, 55.

6.2. (*R*,*E*)-1-(4-Methoxyphenyl)non-2-en-1-ol

According to the general procedure, 1-octyne (0.260 mL, 1.5 mmol), *p*-methoxybenzaldehyde (0.12 mL, 1 mmol), and diethylzinc afforded 0.22 g (90% based on the aldehyde) of the title compound as a colorless oil. HPLC (Chiracel OD-H, *n*-heptane/*i*-PrOH = 97:3): 98.1% ee (*R*) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.4 Hz, 3H, CH_3), 1.23–1.43 (m, 6H), 2.00–2.08 (m, 2H, $CHCH_2CH_2$), 5.10 (d, br, J = 6.6 Hz, 1H, $ArCH(OH)CH$), 5.61–5.78 (m, 2H, $CH(OH)CHCH$), 6.88 (d, br, J = 9.9 Hz, 3H, HAr), 7.28 (d, br, J = 9.9 Hz, 2H, HAr) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09, 22.61, 28.88, 29.08, 31.70, 32.20, 55.28, 74.75, 113.84, 127.46, 132.35, 132.43, 135.73, 159.00 ppm.

6.3. (*R*,*E*)-1-(2-Chloro-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μL, 1 mmol), 2-chlorobenzaldehyde (56.0 μL, 0.5 mmol), and diethylzinc afforded 100 mg (90% yield based on the aldehyde) of (*R*)-1-(2-chlorophenyl)-hept-2-en-1-ol as a colorless oil. HPLC (Chiracel OD-H, *n*-heptane/*i*-PrOH = 97:3): 98.1% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.0 Hz, CH_3), 1.39–1.27 (m, 4H), 2.07–2.03 (m, 2H, $CHCH_2CH_2$), 5.56 (d, 1H, J = 7.0 Hz, $ArCH(OH)CH$), 5.65 (dd, 1H, J = 15.0, 6.5 Hz, $CH(OH)CHCH$), 5.79 (dt, 1H, J = 15.0, 7.0 Hz, $CHCHCH_2$), 7.20 (t, 1H, J = 7.8 Hz, HAr), 7.34–7.27 (m, 2H, HAr), 7.56 (d, 1H, J = 8.0 Hz, HAr). ^{13}C (100 MHz, $CDCl_3$) δ 14.06, 22.35, 31.29, 32.04, 71.62, 127.23, 127.56, 128.65, 129.61, 130.29, 132.43, 133.60, 140.81 ppm.

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