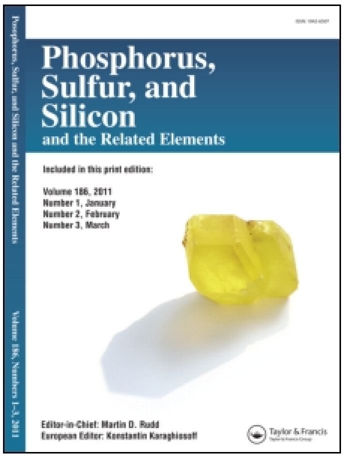

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# Synthesis of Novel Chiral Thioether Ligands Containing Imidazole Rings Based on Natural Amino Acids

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# SYNTHESIS OF NOVEL CHIRAL THIOETHER LIGANDS CONTAINING IMIDAZOLE RINGS BASED ON NATURAL AMINO ACIDS

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***Using commercially available natural amino acids (L-Val, L-Leu, L-Phe) as chiral precursors, a series of N-substituted imidazole derivatives containing chiral groups was synthesized from the condensation reaction of amino acids, formaldehyde, glyoxal, and ammonia. Through esterification, reduction, chlorination, and subsequent substitution by thiols, chiral thioethers containing imidazole rings were synthesized, and the synthetic conditions were optimized. All the intermediates and the final products were characterized by NMR, ESI MS, HR MS, and IR.***

**Keywords** Chiral ligands; imidazole derivatives; natural amino acids; thioethers

## INTRODUCTION

Due to the high coordination ability of the sulfur atom to most transition metals, sulfur donor ligands have been interestingly applied in transition metal–catalyzed homogeneous processes, and the most successful examples belong to chelates.[1–4] An extensive series of S, X- (X = N, P, O, etc.) heterodonor ligands, which can provide a variety of electronic and steric properties, have been developed.[5–9] Compared to the widely used phosphine ligands, sulfur ligands are poor $\sigma$-donor and $\pi$-acceptor ligands, while the trans-effect of sulfur ligands was found to be higher than those of nitrogen- and oxygen-containing ligands. Moreover, sulfur-containing ligands feature the advantages of easy availability and high stability, allowing convenient storage and handling compared to phosphine derivatives. Furthermore, chelating asymmetrically disubstituted thioether ligands opens new possibilities over other chelates because a new stereogenic center is formed at the sulfur by coordination to a metal. Although the low inversion barrier (10–15 kcal$\cdot$mol$^{-1}$) sometimes leads to difficult control of the new stereogenic center, a chiral center close to the sulfur atom may control the new chiral center effectively when the sulfur atom coordinates to a transition metal. In additional, a sulfur atom in a thioether has only two substitutents,

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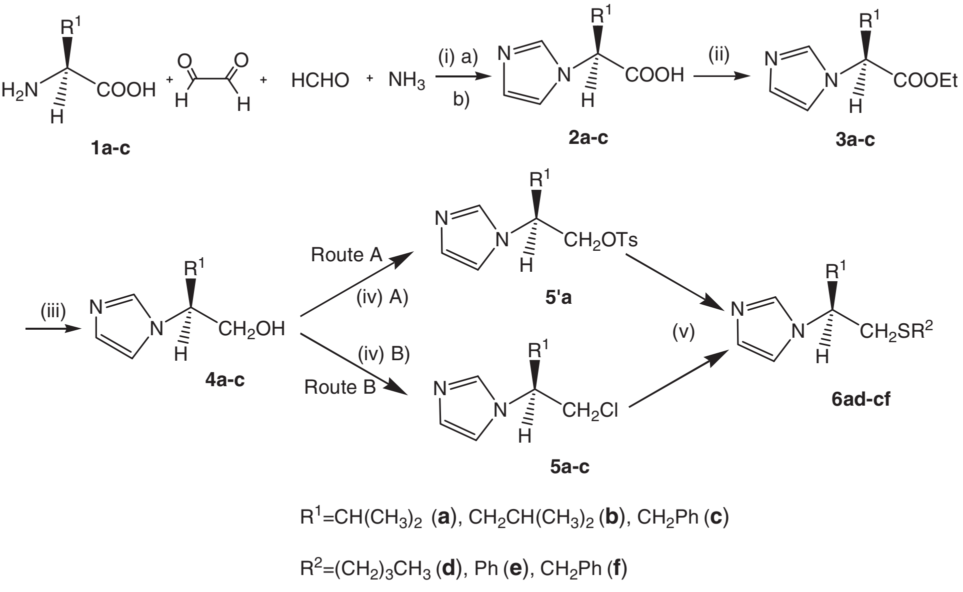
creating a less hindered environment than trivalent phosphorous. A diverse array of chiral sulfur-containing ligands has been synthesized and applied in coordination chemistry and asymmetric catalysis.

N-heterocyclic carbenes (NHCs) derived from imidazolium salts have emerged as a very powerful class of ligands. A series of chelating carbenes generated from imidazole derivatives carrying N-substituents with different donor atoms (X = N, P, S, etc.) has been widely used in organometallic chemistry and homogeneous catalysis.[10–16] However, chiral chelating sulfur ligands containing a potential carbene center have been less extensively explored.[17,18] In this article, we report for the first time the preparation and characterization of a series of chiral thioether ligands containing an imidazole ring, which may be further utilized as a precursor of chiral bidentate sulfur, carbine ligands for organometallic chemistry and homogeneous catalysis, or functionalized chiral ionic liquids.

## RESULTS AND DISCUSSION

For the synthesis of imidazole derivatives, Heinrich Debus first reported a “three component–one pot” reaction, in which condensation of ammonia, formaldehyde, and glyoxal afforded C-2 substituted imidazole.[19] Yet the yields were usually quite low. Arduengo III et al.[20] made an adaption of Debus’s method and proposed a “four component–one pot” procedure, in which combination of formaldehyde, glyoxal, ammonia, and an amine could produce optionally substituted imidazole derivatives, and the yields were improved.

Our synthesis procedure is shown in Scheme 1. A slight modification of the “four component–one pot” method was used to form the imidazole ring. By using a chiral amino



**Scheme 1** Synthesis of thioether ligands. *Reagents and conditions*: (i) a) NaOH (aq), 50°C, 8 h; b) HCl (5 mol/L); (ii) Cat., 4 Å molecular sieve, EtOH, reflux, 12 h; (iii) $NaBH_4$, EtOH, 0°C-reflux overnight; (iv) A) TsCl, $Et_3N$, THF, reflux overnight; B) $Na_2CO_3$, $SOCl_2$, 45°C, 5 h, reflux 2 h; (v) NaOH, $R^2SH$, EtOH, reflux overnight.

**Table I** Results of esterification using different catalysts

| Entry | Catalyst | Yield[a] |
|---|---|---|
| 1[b] | $NaHSO_4$ | 67% |
| 2 | Cation exchange resin | 65.5% |
| 3 | $NaHSO_4$ & cation exchange resin | 81% |
| 4 | $CuSO_4 \cdot 5H_2O$ | 53% |
| 5 | $FeCl_3 \cdot 6H_2O$ | 40% |
| 6[c] | $SOCl_2$ | 71.3% |

[a] Isolated yield over two steps based on **1a** used.

[b] Entries 1–5 were all performed using the follow reaction conditions: (i) 0.06 mol of **1a**, 0.06 mol of glyoxal water solution, 0.06 mol of formaldehyde water solution, 0.06 mol of NaOH, 12 mL $H_2O$, 50°C, 8 h; (ii) 0.06 mol cat., except that cation exchange resin was 2 g, 150 mL EtOH, reflux, 12 h.

[c] Entry 6 was performed as follows: (i) Same with entries 1–5; (ii) 20 mL of $SOCl_2$, 0°C–r.t. overnight.

acid instead of an amine, an imidazole containing an appended chiral functionality was produced. Because the chiral center did not directly participate in the condensation, there was little risk for the racemization/epimerization of the chiral center.[21] From compounds **1a–c** (L-Val, L-Leu, L-Phe), imidazole derivatives **2a–c** carrying an N-substitutent with a chiral center were obtained, which were then treated successively by esterification, reduction, chlorination, and substitution by thiols to afford thioethers **6ad–cf**.

Without separation of **2a–c** from the reaction mixture, the esterification was carried out to produce compounds **3a–c**. Several catalysts have been tested in the esterification of **3a** in ethanol (Table I). The combination of $NaHSO_4$ and cation exchange resin were chosen for the esterification due to its advantages of mild reaction condition, simple workup procedure, and high yields (81%). Additionally, a cation exchange resin could be recycled. $SOCl_2$ produced a yield of 71%, while the harsh reaction conditions required and the odoriferous gases (HCl, $SO_2$) released during the reaction limited its application. Although inorganic salt catalysts, such as $CuSO_4 \cdot 5H_2O$ and $FeCl_3 \cdot 6H_2O$, were convenient to use, these catalyst systems usually produce plenty of floccules, resulting in difficult workup procedure and low separation yields.

To obtain alcohols **4a–c**, esters **3a–c** were reduced by $NaBH_4$, which has the advantages of mild reaction conditions, simple workup, and low costs. Although $LiAlH_4$ was more often used due to its high reactivity, it has the disadvantage of requiring harsh reaction conditions. In addition, it usually forms plenty of floccules during the reaction, which results in low separation yields. In our case, reduction of **3a–c** by $NaBH_4$ in anhydrous EtOH afforded **4a–c** with separation yields between 65–75%.

To synthesize the target compounds **6**, two commonly used procedures for the synthesis of thioethers were investigated (Scheme 1, routes A and B).[22–24] As the tosylation of alcohols was a common transformation usually used to facilitate subsequent substitution reaction, we first used route A for the synthesis of compounds **6**. **5′a** was obtained with a yield of 28%, which was much lower than reported in the literature (78–97%).[25] This was tentatively attributed to the high reactivity of the sulfonate and the strong basicity of N-3 ($pK_b = 6.95$) in compound **5′**, which led to the inter-substitution reaction and resulted in the quarternization of compound **5′a**.

To avoid the inter-substitution reaction, we chose relatively low reactive intermediates chlorides instead of sulfonates (route B). In addition, route B had the merit of simple workup of the reaction mixture, and intermediates **5** could react with thiols to produce thioethers without separation. Maybe due to the low conversion of chlorides to thioethers, the yields of **6** were only acceptable, not high.

## CONCLUSION

We developed a highly versatile method for the synthesis of chiral thioether ligands containing an imidazole ring using natural amino acids as chiral precursors. Investigation of different routes showed that by tuning the reactivity of the intermediates, thioethers were obtained with reasonable yields. Tuning the reaction conditions to obtain thioethers containing different numbers of imidazole rings for transition metal catalysis is now under investigation, and the results will be published in due course.

## EXPERIMENTAL

All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification unless stated otherwise. All reactions were carried out under atmosphere. The products were purified by column chromatography using silica gel (100–200 mesh), and visualization was accomplished by $I_2$ staining. NMR spectra were recorded in $CDCl_3$ on a Bruker 400 MHz spectrometer. The chemical shifts were reported as ppm downfield using TMS as internal standard. Mass spectra (MS) were measured on Bruker Esquire 3000 ESI MS. High resolution mass spectra (HR MS) were obtained on a Waters Micromass Q-Tof Micro instrument using the ESI technique. IR spectra were recorded on a Nicolet Spectrum 2000 infrared spectrophotometer using KBr pellets. Molar optical rotations were measured on a WZZ-2B digital polarimeter.

### General Procedure to Prepare Compounds 3a–c

A formaldehyde/water solution (36% w/v, 4.6 mL, 0.06 mol) and aqueous glyoxal (40% w/v, 7.6 mL, 0.06 mol) were mixed before an ammonia (25% w/v, 6.8 mL, 0.09 mol) and sodium hydroxide solution (10% w/v, 24 mL, 0.06 mol) containing L-Val **1a** (7.03 g, 0.06 mol) was added dropwise. The mixture was stirred at 50°C for 8 h before hydrochloric acid (5 mol/L) was added to adjust the pH to 1–2. Water was then evaporated, and the residue was dried under vacuum at 60°C to afford the crude product **2a**.

Compound **2a** and sodium hydrosulfate (7.20 g, 0.06 mol) were dissolved in anhydrous ethanol (150 mL), then cation ion exchange resin (2 g) was added, and the mixture was heated to reflux for 12 h before being filtered. The filtrate was evaporated, and the residue was dissolved in water. The pH value was adjusted to 8–9 by saturated aqueous sodium bicarbonate solution before being extracted with ethyl acetate (3 × 20 mL). The combined organic phase was concentrated and purified by silica column chromatography (petroleum ether:ethyl acetate, 3:1 v/v) to afford **3a**. Compounds **3b–c** were prepared by similar procedures, and characterization data of **3a,b** are consistent with the literature.[26]

**Compound 3c:** Purified by silica column chromatography (petroleum ether:ethyl acetate, 3:1 v/v). Yield: 83%; yellow oil; $[\alpha]_D^{25}$ (c = 2.0, EtOH): –39.2; IR ($\nu$ cm$^{-1}$): 3381 (N—H), 3112 (=C—H), 2962 (C—H); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.41(s, 1H, $H_{imi\text{-}2}$), 7.21–7.19 (m, 3H, $H_{imi}$ & $H_{Ar}$), 6.98–6.04 (m, 4H, $H_{Ar}$), 4.92–4.89 (m, 1H, NCH), 4.17 (q, $J = 7.2$ Hz, 2H, $OC\underline{H_2}CH_3$), 3.42–3.17 (m, 2H, $PhC\underline{H_2}$), 1.22 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H_3}$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 169.1 (C=O), 136.9 ($C_{imi\text{-}2}$), 135.4, 129.3, 128.7, 127.3, 126.6, 118.1, 62.0 ($N\underline{C}HCO$), 61.4 ($O\underline{C}H_2CH_3$), 39.6 ($\underline{C}H_2Ph$), 13.9 ($OCH_2\underline{C}H_3$); ESI MS m/z : 244.6 $[M + H]^+$.

## General Procedure to Prepare Compounds 4a–c

Compound **3a** (11.80 g, 0.06 mol) was dissolved in anhydrous ethanol (60 mL). The solution was cooled to 0°C, and sodium borohydride (9.08 g, 0.24 mol) was added. The mixture was then heated to reflux overnight. Water (20 mL) was added, and the pH was regulated by sodium hydroxide to 14 before being extracted by ethyl acetate (3 × 20 mL). The crude product was purified by silica column chromatography (ethyl acetate:alcohol, 18:1 v/v), and **4a** was obtained. Compounds **4b–c** were prepared by similar procedures. The characterization data of **4a,b** are consistent with literature.[26]

**Compound 4c:** Purified by silica column chromatography (ethyl acetate:alcohol, 11:1 v/v), yield: 65%; light yellow solid; mp 75–77°C; $[\alpha]_D^{25}$ (c = 2.0, EtOH): –109.5; IR ($\nu$ $cm^{-1}$): 3401 (N—H), 3156 (=C—H), 2938 (C—H); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.26–6.87 (m, 8H, $H_{imi}$ & $H_{Ar}$), 5.62 (bs, 1H, OH), 4.25–4.19 (m, 1H, NCH), 3.85–3.79 (m, 2H, $C\underline{H_2}OH$), 3.17–3.12 (m, 1H, $PhC\underline{H_2}$), 3.00–2.84 (m, 1H, $PhC\underline{H_2}$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 137.1 ($C_{imi\text{-}2}$), 136.4, 128.8, 128.8, 128.3, 127.3, 117.6, 63.9 ($\underline{C}H_2OH$), 62.1 ($N\underline{C}HCH_2OH$), 38.4 ($\underline{C}H_2Ph$); ESI MS m/z : 202.6 $[M + H]^+$.

## Procedure to Prepare Compound 5′a

In a 100 mL flask**,** **4a** (0.39 g, 2.50 mmol), triethylamine (0.7 mL, 5 mmol), and tosyl chloride (0.72 g, 3.75 mmol) were dissolved in tetrahydrofuran (15 mL). The mixture was heated to reflux, and the reaction was followed by TLC detection until the starting material disappeared. The mixture was then filtered. The filtrate was concentrated and purified by silica column chromatography (chloroform:acetone, 5:1 v/v). **5′a** was obtained with a yield of 28%; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.64 (d, $J = 8.3$ Hz, 2H, $H_{Ar}$), 7.48 (s, 1H, $H_{imi\text{-}2}$), 7.32 (d, $J = 8.0$ Hz, 2H, $H_{Ar}$), 7.02 (s, 1H, $H_{imi}$), 6.84 (s, 1H, $H_{imi}$), 4.29–4.27 (m, 2H, $NCHC\underline{H_2}O$), 3.91–3.88 (m, 1H, NCH), 2.45 (s, 3H, $PhC\underline{H_3}$), 2.15–2.09 (m, 1H, $C\underline{H}(CH_3)_2$), 1.01 (d, $J = 6.6$ Hz, 3H, $CH(C\underline{H_3})_2$), 0.75 (d, $J = 6.7$, 3H, $CH(C\underline{H_3})_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 145.4 ($C_{Ph\text{-}4'}$), 139.9 ($C_{imi\text{-}2}$), 132.0, 130.1, 128.8, 127.9, 125.9, 69.6 ($\underline{C}H_2OSO_2$), 55.0 ($N\underline{C}HCH_2O$), 30.0 ($C\underline{H_2}Ph$), 21.5 ($\underline{C}H(CH_3)_2$), 19.5 ($CH(\underline{C}H_3)_2$); ESI MS m/z: 308.8 $[M + H]^+$.

## General Procedure to Prepare Compounds 6ad–cf

To a 100 mL flask containing **4a** (1.54 g, 0.01 mol) and sodium carbonate (1.06 g, 0.01 mol), thionyl chloride (20 mL) was added dropwise at 45°C. The mixture was kept at 45°C for 5 h before being heated to reflux for 2 h. The excessive thionyl chloride was removed under reduced pressure. The residue was dissolved in water (10 mL), and the pH was regulated to 7 by sodium bicarbonate before being extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous sodium sulfate. After filtration and concentration, **5a** was produced.

In a 100 mL flask, sodium hydroxide (1.20 g, 0.03 mol) and thiophenol (3.0 mL, 0.03 mol) were dissolved in ethanol (30 mL), and the solution was heated to 50°C. An ethanol solution (20 mL) of **5a** was added dropwise, and the mixture was heated to reflux overnight. The solvent was removed under reduced pressure, and the residue was extracted by ether (3 × 10 mL). The crude product was purified by silica column chromatography (petroleum ether:ethyl acetate, 2:3 v/v), and **6ad** was obtained. Compounds **6ae–cf** were prepared by similar procedures.

**Compound 6ad:** Yellow oil; yield: 23.2%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +17.6; IR ($\nu$ cm$^{-1}$): 3105 (=C—H), 2990 (C—H), 2735 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.51 (s, 1H, $H_{imi\text{-}2}$), 7.23 (s, 1H, $H_{imi}$), 6.94 (s, 1H, $H_{imi}$), 3.81–3.76 (m, 1H, NCH), 2.98 (d d, $J$ = 13.8 Hz, $J$ = 4.2 Hz, 1H, $NCHC\underline{H}_2S$), 2.85 (d d, $J$ = 13.8 Hz, $J$ = 9.2 Hz, 1H, $NCHC\underline{H}_2S$), 2.28 (t, $J$ = 7.2 Hz, 2H, $SC\underline{H}_2CH_2CH_2CH_3$), 2.15–2.06 (m, 1H, $C\underline{H}(CH_3)_2$), 1.50–1.43 (m, 2H, $SCH_2C\underline{H}_2CH_2CH_3$), 1.38–1.26 (m, 2H, $SCH_2CH_2C\underline{H}_2$ $CH_3$), 1.02 (d, $J$ = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.87 (t, $J$ = 7.3 Hz, 3H, $SCH_2CH_2CH_2C\underline{H}_3$), 0.79 (d, $J$ = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 137.1 ($C_{imi\text{-}2}$), 129.2, 117.2, 65.3 ($N\underline{C}HCH(CH_3)_2$), 35.7, 32.7, 32.3, 31.6, 21.8, 20.0, 18.7, 13.6; HR MS m/z: 227.1501 [M + H]$^+$ (calculated for $C_{12}H_{22}N_2O$ 226.1504).

**Compound 6ae:** Yellow oil; yield: 31.5%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +62.0; IR ($\nu$ cm$^{-1}$): 3341 (N—H), 3098 (=C—H), 2980 (C—H), 2730 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.42 (s, 1H, $H_{imi\text{-}2}$), 7.28–7.20 (m, 5H, $H_{Ar}$), 7.06 (s, 1H, $H_{imi}$), 6.86 (s, 1H, $H_{imi}$), 3.79–3.74 (m, 1H, $NC\underline{H}$), 3.46 (d d, $J$ = 13.9 Hz, $J$ = 4.2 Hz, 1H, $CH_2S$), 3.16 (d d, $J$ = 9.8 Hz, $J$ = 4.2 Hz, 1H, $CH_2S$), 2.16–2.04 (m, 1H, $C\underline{H}(CH_3)_2$), 0.99 (d, $J$ = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.77 (d, $J$ = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 137.3 ($C_{imi\text{-}2}$), 134.8, 130.5, 129.4, 129.1, 127.0, 117.1, 63.6 ($N\underline{C}HCH_2S$), 38.1 ($NCH\underline{C}H_2S$), 32.9 ($\underline{C}H(CH_3)_2$), 20.0, 18.7; HR MS m/z: 247.1189 [M + H]$^+$ (calculated for $C_{14}H_{18}N_2O$ 246.1191).

**Compound 6af:** Yellow oil; yield: 29.4%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +37.0; IR ($\nu$ cm$^{-1}$): 3380 (N—H), 3112 (=C—H), 2985 (C—H), 2743 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.42 (s, 1H, $H_{imi\text{-}2}$), 7.33–7.21 (m, 5H, $H_{Ar}$), 7.07 (s, 1H, $H_{imi}$), 6.84 (s, 1H, $H_{imi}$), 3.59–3.53 (m, 1H, NCH), 3.49–3.40 (m, 2H, $SC\underline{H}_2Ph$), 2.86 (d d, 1H, $J$ = 14.1 Hz, $J$ = 4.0 Hz, $NCHC\underline{H}_2S$), 2.69 (d d, 1H, $J$ = 14.0 Hz, $J$ = 9.6 Hz, $NCHC\underline{H}_2S$), 2.06–1.93 (m, 1H, $C\underline{H}(CH_3)_2$), 0.88 (d, 3H, $J$ = 6.7 Hz, $CH_3$), 0.69 (d, 3H, $J$ = 6.7 Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 137.9 ($C_{imi\text{-}2}$), 137.1, 129.2, 128.9, 128.5, 127.2, 117.2, 64.7 ($N\underline{C}HCH_2S$), 36.6 ($PhC\underline{H}_2S$), 34.8 ($NCH\underline{C}H_2S$), 32.7 ($\underline{C}H(CH_3)_2$), 19.9, 18.7; HR MS m/z: 261.1341 [M + H]$^+$ (calculated for $C_{15}H_{20}N_2O$ 260.1347).

**Compound 6bd:** Yellow oil; yield: 35.6%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): –10.7; IR ($\nu$ cm$^{-1}$): 3363 (N—H), 3100 (=C—H), 2965 (C—H), 2710 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.54 (s, 1H, $H_{imi\text{-}2}$), 7.10 (bs, 2H, $H_{imi}$), 4.19–4.14 (m, 1H, NCH), 2.85–2.74 (m, 2H, $NCHCH_2S$), 2.25 (t, $J$ = 7.2 Hz, 2H, $SC\underline{H}_2CH_2CH_2CH_3$), 1.83–1.64 (m, 2H, $C\underline{H}_2CH(CH_3)_2$), 1.50–1.30 (m, 5H, $SCH_2C\underline{H}_2C\underline{H}_2CH_3$ & $C\underline{H}(CH_3)_2$), 0.91–0.86 (m, 9H, $3CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 136.5 ($C_{imi\text{-}2}$), 129.6, 116.5, 57.2 ($N\underline{C}HCH_2S$), 43.7, 39.0, 32.5, 31.6, 24.6, 23.0, 21.8, 21.6, 13.6; HR MS m/z: 241.1657 [M + H]$^+$ (calculated for $C_{13}H_{24}N_2O$ 240.1660).

**Compound 6be:** Yellow oil; yield: 38.8%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +57.7; IR ($\nu$ cm$^{-1}$): 3375 (N—H), 3107 (=C—H), 2956 (C—H), 2710 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.45 (s, 1H, $H_{imi\text{-}2}$), 7.28–7.23 (m, 5H, $H_{Ar}$), 7.05 (s, 1H, $H_{imi}$), 6.87 (s, 1H, $H_{imi}$), 4.16–4.10 (m, 1H, $NC\underline{H}$), 3.23 (d d, $J$ = 13.8 Hz, $J$ = 5.7 Hz, 1H, $CH_2S$), 3.14 (d d, $J$ = 13.8 Hz, $J$ = 7.9 Hz, 1H, $CH_2S$), 1.82–1.68 (m, 2H, $C\underline{H}_2CH(CH_3)_2$), 1.36–1.26

(m, 1H, $C\underline{H}(CH_3)_2$), 0.84 (d, $J = 5.0$ Hz, 3H, $CH(C\underline{H}_3)_2$), 0.83 (d, $J = 5.0$ Hz, 3H, $CH(C\underline{H}_3)_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 136.6 ($C_{imi-2}$), 134.7, 130.4, 129.7, 129.2, 127.0, 116.3, 55.7 ($N\underline{C}HCH_2S$), 43.7 ($\underline{C}H_2CH(CH_3)_2$), 41.2 ($NCH\underline{C}H_2S$), 24.6, 23.0, 21.5; HR MS m/z: 261.1342 [M + H]$^+$ (calculated for $C_{15}H_{20}N_2O$ 260.1347).

**Compound 6bf:** yellow oil; yield: 37.6%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +31.5; IR ($\nu$ cm$^{-1}$): 3350 (N—H), 3098 (=C—H), 2981 (C—H), 2723 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.41 (s, 1H, $H_{imi-2}$), 7.34–7.23 (m, 5H, $H_{Ar}$), 7.08 (s, 1H, $H_{imi}$), 6.85 (s, 1H, $H_{imi}$), 3.93–3.89 (m, 1H, NCH), 3.50–3.39 (m, 2H, $SC\underline{H}_2Ph$), 2.71 (d d, 1H, $J = 14.1$ Hz, $J = 5.6$ Hz, $NCHC\underline{H}_2S$), 2.64 (d d, 1H, $J = 14.1$ Hz, $J = 7.9$ Hz, $NCHC\underline{H}_2S$), 1.73–1.66 (m, 1H, $C\underline{H}_2CH(CH_3)_2$), 1.60–1.53 (m, 1H, $C\underline{H}_2CH(CH_3)_2$), 1.27–1.24 (m, 1H, $C\underline{H}(CH_3)_2$), 0.80 (t, $J = 12.4$ Hz, 6H, $2CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 138.0 ($C_{imi-2}$), 136.6, 129.6, 128.9, 128.6, 127.3, 116.4, 56.7 ($N\underline{C}HCH_2S$), 43.5 ($C\underline{H}_2CH(CH_3)_2$), 38.1 ($PhC\underline{H}_2S$), 36.9 ($NCH\underline{C}H_2S$), 24.5, 23.1, 21.4; HR MS m/z: 275.1498 [M + H]$^+$ (calculated for $C_{16}H_{22}N_2O$ 274.1504).

**Compound 6cd**: Yellow oil; yield: 79.8%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): –41.8; IR ($\nu$ cm$^{-1}$): 3110 (=C—H), 2950 (C—H), 2700 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: (m, 8H, $H_{imi}$ & $H_{Ar}$), 4.31–4.27 (m, 1H, $NC\underline{H}$), 3.23 (d d, $J = 13.8$ Hz, $J = 5.8$ Hz, 1H, $C\underline{H}_2Ph$), 3.04 (d d, $J = 13.8$ Hz, $J = 8.5$ Hz, 1H, $C\underline{H}_2Ph$), 2.94–2.83 (m, 2H, $NCHC\underline{H}_2$), 2.29 (t, $J = 7.4$ Hz, 2H, $SC\underline{H}_2CH_2CH_2CH_3$), 1.48–1.30 (m, 4H, $SCH_2C\underline{H}_2$ $C\underline{H}_2CH_3$), 0.87 (t, $J = 7.3$ Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 136.7 ($C_{imi-2}$), 136.5, 129.6, 128.8, 128.7, 127.0, 116.6, 60.5 ($N\underline{C}HCH_2S$), 55.7 ($\underline{C}H_2Ph$), 43.8 ($NCH\underline{C}H_2S$), 41.4, 37.4, 32.4, 31.6, 21.8, 13.6; HR MS m/z: 275.1498 [M + H]$^+$ (calculated for $C_{16}H_{22}N_2O$ 274.1504).

**Compound 6ce**: Yellow oil; yield: 47.5%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): +104.0; IR ($\nu$ cm$^{-1}$): 3348 (N—H), 3109 (=C—H), 2924 (C—H), 2810 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.28–6.86 (m, 13H, $H_{imi}$ & $H_{Ar}$), 4.27–4.20 (m, 1H, NCH), 3.36–3.00 (m, 4H, $NCHC\underline{H}_2S$ & $C\underline{H}_2Ph$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 136.6 ($C_{imi-2}$), 136.4, 134.4, 130.3, 129.6, 129.2, 128.8, 128.7, 127.1, 127.0, 116.5, 59.2 ($N\underline{C}HCH_2S$), 41.5, 39.4; HR MS m/z: 295.1189 [M + H]$^+$ (calculated for $C_{18}H_{18}N_2O$ 294.1191).

**Compound 6cf**: Yellow oil; yield: 45.6%; $[\alpha]_D^{25}$ (c = 2.0, EtOH): –67.0; IR ($\nu$ cm$^{-1}$): 3280 (N—H), 3098 (=C—H), 2900 (C—H), 2710 ($CH_2$—S); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.39 (s, 1H, $H_{imi-2}$), 7.37–6.85 (m, 12H, $H_{imi}$ & $H_{Ar}$), 4.07–4.03 (m, 1H, NCH), 3.51–3.43 (m, 2H, $SC\underline{H}_2Ph$), 3.13 (d d, 1H, $J = 13.8$ Hz, $J = 6.0$ Hz, $NCHC\underline{H}_2S$), 2.94 (d d, 1H, $J = 13.8$ Hz, $J = 8.4$ Hz, $NCHC\underline{H}_2S$), 2.81 (d d, 1H, $J = 14.1$ Hz, $J = 5.7$ Hz, $NCHC\underline{H}_2Ph$), 2.73 (d d, 1H, $J = 14.1$ Hz, $J = 7.8$ Hz, $NCHC\underline{H}_2Ph$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 137.9 ($C_{imi-2}$), 136.6, 136.5, 129.3, 129.0, 128.9, 128.8, 128.67, 128.5, 127.3, 127.0, 116.6, 60.2 ($N\underline{C}HCH_2S$), 41.4, 36.8, 36.5; HR MS m/z: 309.1345 [M + H]$^+$ (calculated for $C_{19}H_{20}N_2O$ 308.1347).

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