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## SYNTHESIS AND CHARACTERIZATION OF *N*-SUBSTITUTED (*S*)-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXAMIDES AND THIOAMIDES AS ORGANOCATALYSTS FOR ASYMMETRIC ALDOL REACTION

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**Abstract** – In this paper, the preparation and characterization of eight optically pure *N*-functionalized (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamides and thioamides is described. The prepared amides and thioamides were tested as organocatalysts of aldol reaction of 4-nitrobenzaldehyde and acetone. The highest ee of formation of 4-hydroxy-4-(4-nitrophenyl)butan-2-one was obtained with (*S*)-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline-3-thiocarboxamide (77% ee). The observed deceleration of the aldol reaction catalyzed in this way, as compared with that catalyzed with (*S*)-proline, was attributed to the formation of little reactive cyclic intermediate, which was isolated and characterized.

*Dedicated to Prof. Dr. Vladimír Macháček on the occasion of his 70<sup>th</sup> birthday*

### INTRODUCTION

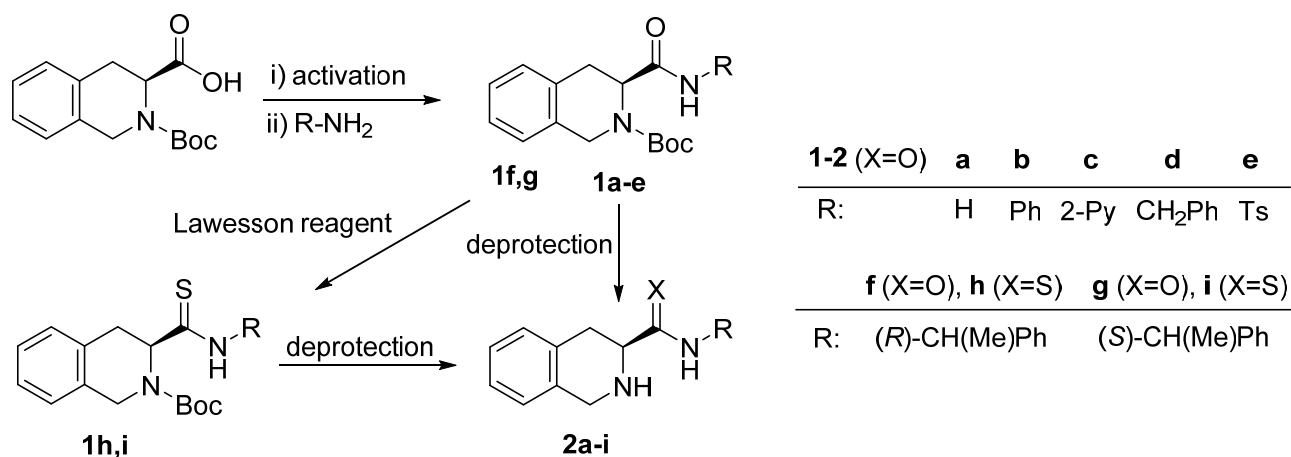
(*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid belongs among the chiral synthetic  $\alpha$ -amino acids that are not found in nature. The acid can be synthesized by Pictet–Spengler reaction of phenylalanine with formaldehyde involving bridge formation between amino group and aromatic nucleus of phenylalanine by means of methylene group.<sup>1</sup> The compounds whose molecules contain an incorporated 1,2,3,4-tetrahydroisoquinoline skeleton exhibit a number of effects on biological systems; e.g., they possess high affinity to opioid receptors,<sup>2,3</sup> or act as inhibitors of some enzymatic reactions.<sup>4–6</sup> In asymmetric

synthesis, the derivatives of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were used as ligands of ruthenium complexes in hydrogenations of ketones (up to 94% ee).<sup>7</sup> The complexes of copper(II) acetate with the oxazolines derived from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were also successfully used as highly enantioselective catalysts for the Henry reaction (up to 77% ee).<sup>8</sup> Moreover, other derivatives of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were proved as useful enantioselective catalysts in the addition reaction of diethylzinc to aldehydes (more than 99% ee).<sup>9</sup> Furthermore, functionalized esters of this acid catalyze the asymmetric Diels–Alder reaction of cinnamic aldehyde with cyclopentadiene (43% ee for the *exo*-product, 50% ee for the *endo*-product, in the ratio of for the *exo:endo*-product).<sup>10</sup> It is known, that in analogy to the molecule of (*S*)-proline, also the molecule (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid possesses a rigid structure, and incorporation of this  $\alpha$ -amino acid into a peptide chain allows preparation of peptides with well-defined tertiary structures.<sup>11</sup> With regard to the similarity with the molecule of (*S*)-proline, it is possible to anticipate analogous properties also for corresponding derivatives of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. This presumption reveals their possible application in organocatalysis. Therefore, the aim of the research work described in this paper was to prepare and characterize a series of new optically pure *N*-functionalized amides and thioamides of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and to test them as organocatalysts of aldol reactions.<sup>11–13</sup>

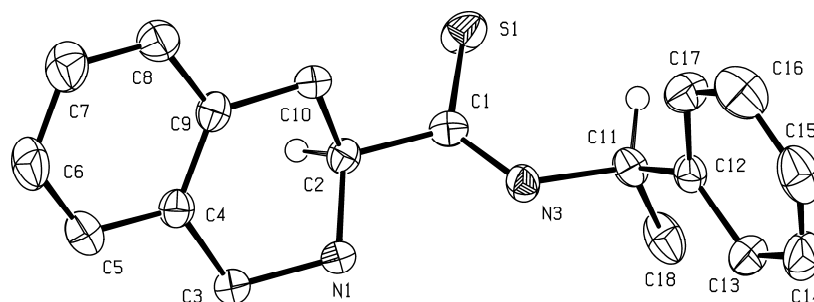
## RESULTS AND DISCUSSION

*N*-Functionalized (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamides (**1a–g**) were prepared by reactions of amines and sulfonamide (aniline, 2-aminopyridine, benzylamine, toluene-4-sulfonamide (*R*)-1-phenylethylamine and (*S*)-1-phenylethylamine) with activated (*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. The activation of carboxylic group was achieved by the action of ethyl chloroformate (Method A) or dicyclohexylcarbodiimide (DCC) (Method B). The yields of functionalized (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamides (**1a–g**) varied in the range 59–65% (Scheme 1).

In the next reaction step, the amides **1f** and **1g** were transformed by the reaction with Lawesson reagent into the corresponding thioamides **1h** (52%) and **1i** (50%). In the last step, the protecting *tert*-butoxycarbonyl group was removed from the prepared amides **1a–g** and thioamides **1h,i** by the reaction with trifluoroacetic acid (TFA). In this way, we prepared (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**2a**)<sup>14</sup> and its *N*-functionalized amides **2b–g** and thioamides **2h,i** in the yields of 68–77%. The structure of derivative **2h** was confirmed by means of X-ray diffraction (Figure 1).

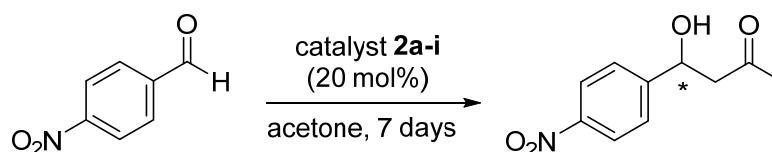


Scheme 1



**Figure 1.** Molecular structure of **2h** (ORTEP view, 50% probability level). Selected interatomic distances [Å] and angles [°]: S1–C1 1.667(2), C1–N3 1.321(3), N3–C11 1.471(3), C1–C2 1.514(3), C2–N1 1.463(3), N1–C3 1.477(3), C3–C4 1.506(3), C4–C9 1.388(3), C9–C10 1.512(3), C10–C2 1.531(3); C1–N3–C11 124.7(2), S1–C1–N3 124.65(18), S1–C1–C2 119.26(17), N3–C1–C2 116.1(2), C1–C2–N1 112.46(18), C2–N1–C3 109.99(18), N1–C3–C4 111.7(2), C3–C4–C9 121.3(2), C4–C9–C10 120.5(2), C9–C10–C2 111.28(19), N1–C2–C10 107.90(19).

Consequently, the catalytic activities of the prepared amides **2a-g** and thioamides **2h,i** were tested and compared with the earlier-described analogous derivatives of (*S*)-proline.<sup>11–13</sup> Enantioselectivities of prepared organocatalysts were studied in the reactions of 4-nitrobenzaldehyde with cyclohexanone and acetone. The aldol reaction was performed in the presence of 20 mol% of organocatalyst at two temperatures (25 °C, –10 °C), the media used being acetone and water/acetone mixtures (Table 1). In order to attain a measurable conversion, it was necessary to evaluate the reactions as late as after 7 days. It turned out, that the reaction of 4-nitrobenzaldehyde with cyclohexanone, in contrast to that with acetone, does not take place even with the application of an equivalent amount of the tested organocatalysts **2a-i**.

**Table 1.** Results of the **2a-i** catalyzed aldol reaction under various conditions

Entry	Catalyst	Solvent	Temperature (°C)	Conversion <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	<b>2a</b>	acetone/H <sub>2</sub> O (20%)	25	98	13
2	<b>2b</b>	acetone/H <sub>2</sub> O (20%)	25	20	12
3	<b>2c</b>	acetone/H <sub>2</sub> O (20%)	25	12	16
4	<b>2d</b>	acetone/H <sub>2</sub> O (20%)	25	92	17
5	<b>2e</b>	acetone/H <sub>2</sub> O (20%)	25	10	39
6	<b>2f</b>	acetone/H <sub>2</sub> O (20%)	25	77	36
7	<b>2g</b>	acetone/H <sub>2</sub> O (20%)	25	86	14
8	<b>2h</b>	acetone/H <sub>2</sub> O (20%)	25	17	77
9	<b>2i</b>	acetone/H <sub>2</sub> O (20%)	25	48	40
10	<b>2b</b>	acetone/H <sub>2</sub> O (20%)	-10	traces	---
11	<b>2c</b>	acetone/H <sub>2</sub> O (20%)	-10	14	19
12	<b>2d</b>	acetone/H <sub>2</sub> O (20%)	-10	56	29
13	<b>2f</b>	acetone/H <sub>2</sub> O (20%)	-10	76	44
14	<b>2g</b>	acetone/H <sub>2</sub> O (20%)	-10	56	15
15	<b>2b</b>	acetone	25	14	17
16	<b>2c</b>	acetone	25	5	---
17	<b>2d</b>	acetone	25	91	17
18	<b>2f</b>	acetone	25	92	21
19	<b>2g</b>	acetone	25	90	5
20	<b>2c</b>	acetone	-10	24	15
21	<b>2d</b>	acetone	-10	23	27
22	<b>2f</b>	acetone	-10	33	31
23	<b>2f</b>	acetone/H <sub>2</sub> O (80%)	25	25	23

<sup>a</sup> The conversion determined by <sup>1</sup>H NMR of crude product.

<sup>b</sup> The enantiomeric excess determined by chiral HPLC using Chiralpak AS-H column.

Table 1 presents the values of conversion and optical yields of aldol reaction obtained under different reaction conditions. The aldol formed was isolated from the reaction mixture by means of column chromatography (SiO<sub>2</sub>, EtOAc/hexane (1/1)). The evaluation showed that a more suitable reaction medium is the acetone/water mixture 80/20 by volume. It was also found that in the presence of trifluoroacetic acid the aldol reaction catalyzed by derivatives **2a-i** did not proceed, although in the case of analogous derivatives of (*S*)-proline, an addition of catalytic amount of trifluoroacetic acid resulted in

an increase from 86% ee to 99% ee.<sup>13</sup> The unsubstituted amide **2a** catalyzed the aldol reaction with the conversion of 98%, but the ee value attained was only 13% (entry 1). The best enantiomeric excess was achieved with the application of thioamide **2h** (77% ee); however, the conversion was only 17% (25 °C) (entry 7). Lowering of the reaction temperature from 25 °C to –10 °C with catalyst **2b** led to stopping of the reaction (entries 2 and 10). With catalysts **2c,d,f**, the temperature decrease caused an only negligible increase in enantiomeric excess, namely from 16% to 19%, from 17% to 29%, and from 36% to 44% (entries 3 and 11, entries 4 and 12, entries 6 and 13, respectively). A significant lowering of conversion was only observed with catalyst **2d** and **2g**, namely from 92% to 56% (entries 4 and 12) resp. from 86% to 56% (entries 7 and 14). A higher content of water in the reaction medium (80% by vol.) in the case of catalyst **2f** resulted in considerable deceleration of reaction, and hence also of conversion (25%) and in lowering of enantioselectivity, as compared with the reaction performed in the mixture acetone/water (20%) (entry 23).

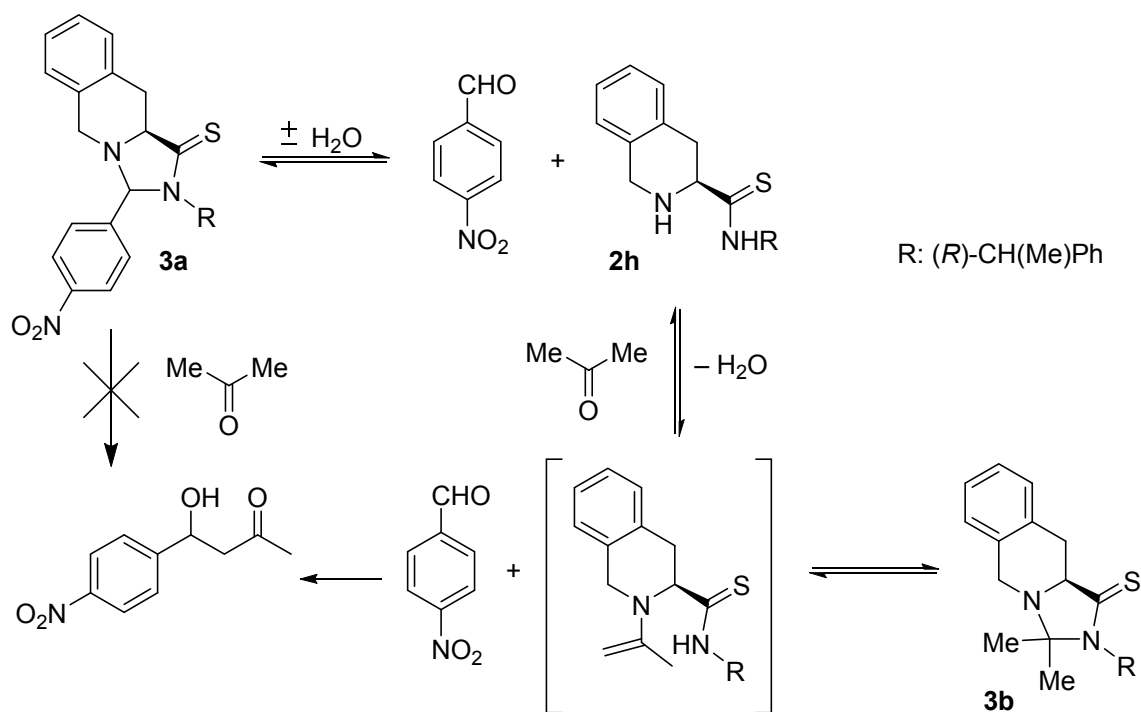
The next group of our organocatalysts (**2h,i**) comprises an isolobal exchange of the amide oxygen atom for sulfur. This structural modification caused a distinct increase in enantioselectivity of the aldol reaction, i.e. 77% ee in the case of thioamide **2h** as compared with 36% ee of amide **2f**. The increase in enantioselectivity can be ascribed to the higher acidity of thioamide functional group as compared with that of amide group (e.g.,  $pK_a$  MeCSNH<sub>2</sub> is 18.5, but that of MeCONH<sub>2</sub> is 25.5).<sup>15</sup> Higher acidity contributes to the formation of the stronger hydrogen bond with the oxygen atom of 4-nitrobenzaldehyde in the transition state of aldol reaction, which leads to increase in stereoselectivity of aldol reaction.<sup>11</sup> For the same reason, a further increase in acidity at the amide nitrogen atom and consequently enantioselectivity (39% ee) was observed in the case of amide **2e** bearing tosyl group. Although the acidity of the derivative **2e** is the highest in this serie, its enantioselectivity is lowered probably due to steric demands of the toluenesulfonic group.

Introduction of another chiral centre into the organocatalyst molecule also increased the enantioselectivity, which was observed in the case of amide **2f** (36% ee) in comparison with amides **2a-e** (max. 17% ee). On the other hand, the presence of the center with opposite configuration (*S*) did not affect enantioselectivity significantly (**2g**, 14% ee). However, a much more significant increase was observed in the analogous case of thioamide **2h** (77% ee) compared with thioamide **2i** (40% ee).

On the basis of the presented results, (*S*)-1,2,3,4-tetrahydroisoquinoline-3-*N*-[(1*R*)-1-phenylethyl]thiocarboxamide (**2h**) represents the best organocatalyst in the given series from the point of enantioselectivity (25 °C, 17%, 77% ee). In the catalysis using the analogous thioamide derived from (*S*)-proline, ((*S*)-*N*-[(1*R*)-1-phenylethyl]pyrrolidine-2-thiocarboxamide), the yield of isolated product was 62% and the enantiomeric excess was 84% at the temperature of 4 °C.<sup>13</sup> These results are comparable from the standpoint of enantioselective effectiveness of the two analogous thioamide catalysts. The

chemical yield obtained with **2h** is significantly lower, as can be explained by general reactivity of corresponding enamines - reactivity of them follows the order pyrrolidine-derived > acyclic-derived > piperidine-derived enamines.<sup>16</sup> On the other hand, in comparison with catalysts **2**, the pipercolinic acid afforded very low catalytic activity (< 10%) and no enantioselectivity for this aldol reaction.<sup>17</sup> Therefore, we consider that the presence of the benzene ring in the structure of the catalysts **2** positive influence their catalytic activity.

Hence, the aldol reaction catalyzed by thioamide **2h** was further studied in more detail (TLC). The reaction of **2h** with 4-nitrobenzaldehyde was used to prepare the cyclic product **3a**, and the reaction with acetone was used to prepare the analogous cyclic product **3b** (Scheme 2). The monitoring of the aldol reaction course showed that, under the conditions of aldol reaction, the reaction mixture contained both cyclic products (**3a** and **3b**). Therefore, the cyclic product **3a** alone was submitted to the reaction with equivalent amount of acetone. In this experiment, the presence of **3b** was observed during the reaction; however, it was subsequently transformed into the product of aldol reaction, i.e. 4-hydroxy-4-(4-nitrophenyl)butan-2-one. From this finding it follows that **3a** has to be decomposed back to the starting **2h** and 4-nitrobenzaldehyde. In analogous way, the cyclic product **3b** alone was submitted to the reaction with equivalent amount of 4-nitrobenzaldehyde.



Scheme 2

It was found that in this reaction, **3b** is only transformed to the product of aldol reaction – most probably *via* enamine.<sup>18</sup> From these findings, summarized in Scheme 2, it is obvious that under the conditions of aldol reaction the operating mechanism is the reversible formation of little reactive intermediate **3a**. This reversible formation of **3a** makes itself felt kinetically as a reaction “blind alley”, which leads to general retardation of the aldol reaction course. A similar occurrence of such mentioned blind reaction pathways was described in the case of *S*-proline derivatives and called “parasitic dead dens”.<sup>18</sup>

## EXPERIMENTAL

All starting substances were purchased from Sigma-Aldrich or Acros. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 400 instrument at the temperatures of 25 °C or 75 °C. Chemical shifts  $\delta$  are referenced to standard Me<sub>4</sub>Si (CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub>,  $\delta$  = 0.00 ppm). The solvent residual peak was used as inner standard for <sup>13</sup>C NMR spectra (77.00 ppm for CDCl<sub>3</sub>, 39.60 ppm for DMSO-*d*<sub>6</sub>). The elemental analysis was carried out using an apparatus FISONs Instruments EA 1108 CHN. The optical rotatory power was measured on a Perkin-Elmer 341 instrument at  $\lambda$  = 589 nm at the temperature of 20 °C, the concentration *c* was given in g/100 mL.

**4-Toluenesulfonic acid benzyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate salt.** To a solution of L-phenylalanine (20 g; 0.12 mol) in conc. HCl (155 mL; 35%; 1.77 mol) was slowly added a solution of formaldehyde in water (37%; 0.60 mol; 45 mL). The mixture was heated to the temperature of 100 °C for 4 h. The solid phase was isolated by filtration after standing for 24 h at the temperature of 25 °C and then washed with water (100 mL) and cold acetone (50 mL) and dried. The crude hydrochloride of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (ca 20 g) was then heated with benzyl alcohol (11 g; 0.1 mol) and 4-toluenesulfonic acid (17.2 g; 0.1 mol) in benzene (180 mL) for 5 h. The pure product (22.4 g; mp 148–150 °C) was obtained after 4 fold recrystallization from aqueous MeOH (80%);  $[\alpha]_D^{20}$  –61.0 (*c* 1.0, MeOH). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm):  $\delta$  2.27 (s, 3H, CH<sub>3</sub>), 3.16 (dd, 1H, H(4a), <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 11.6 Hz), 3.32 (dd, 1H, H(4b), <sup>2</sup>*J* = 17.1 Hz, <sup>3</sup>*J* = 5.0 Hz), 4.34–4.44 (m, 2H, H(1a) + H(1b)), 4.67 (dd, 1H, H(3), <sup>3</sup>*J* = 11.6 Hz, <sup>3</sup>*J* = 5.0 Hz), 5.30 (s, 2H, CH<sub>2</sub>), 7.09–7.11 (m, 2H, Ar), 7.25–7.27 (m, 4H, Ar), 7.35–7.48 (m, 7H, Ar), 9.78 (s, 2H, NH<sub>2</sub><sup>+</sup>). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, ppm):  $\delta$  20.9, 28.01, 44.2, 53.4, 67.5, 125.6, 126.7, 127.01, 127.8, 128.3, 128.2, 128.6, 128.7, 128.9, 130.4, 135.2, 138.0, 145.4, 168.5. Anal. Calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>5</sub>S (439.5): C, 65.58; H, 5.73; N, 3.19; S, 7.30. Found: C, 65.29; H, 5.59; N, 3.12; S, 6.99.

**Benzyl 2-*tert*-butyl (*S*)-1,2,3,4-tetrahydroisoquinoline-2,3(1*H*)-dicarboxylate.** 4-Toluenesulfonic acid benzyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate salt (18 g; 0.04 mol) was neutralized with aqueous solution of NaHCO<sub>3</sub> (8%; 0.14 mol) and extracted with EtOAc (3 × 50 mL). The organic extract

was washed with saturated solution of  $\text{NH}_4\text{Cl}$  ( $1 \times 50$  mL), with water ( $3 \times 50$  mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The obtained free base of benzyl ester was acylated with di-*tert*-butyl dicarbonate (10.5 g; 0.048 mol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) at the temperature of 25 °C for 2 h. The reaction mixture was then washed with aqueous solution of citric acid (10%; 50 mL), water ( $2 \times 50$  mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Yield 13.9 g (95%) as oil.  $[\alpha]_{\text{D}}^{20} -2.2$  ( $c$  1.1, MeOH).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , ppm, 75 °C):  $\delta$  1.44–1.56 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 3.16–3.20 (m, 1H,  $H(4a)$ ), 3.29–3.34 (m, 1H,  $H(4b)$ ), 4.54–4.58 (m, 1H,  $H(1a)$ ), 4.69–4.74 (m, 1H,  $H(1b)$ ), 4.86–5.25 (m, 3H,  $\text{CH}_2$  a  $H(3)$ ), 7.10–7.25 (m, 6H, *Ar*), 7.29–7.32 (m, 3H, *Ar*).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , ppm, 75 °C):  $\delta$  27.5, 30.4, 43.5, 54.6, 65.5, 79.3, 125.5, 126.1, 126.2, 126.9, 127.3, 127.7, 131.5, 135.5, 170.6. Anal. Calcd for  $\text{C}_{22}\text{H}_{25}\text{NO}_4$  (367.4): C, 71.91; H, 6.86; N, 3.81. Found: C, 71.85; H, 6.79; N, 3.90.

**(*S*)-2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.** The mixture of benzyl 2-*tert*-butyl (*S*)-1,2,3,4-tetrahydroisoquinoline-2,3(1*H*)-dicarboxylate (10.6 g; 28.9 mmol), Pd/C (0.5 g; 5%) in EtOAc (150 mL) was stirred under hydrogen atmosphere (ca 5 kPa) at the temperature of 25 °C for 24 h. The catalyst was removed by filtration and the solvent was evaporated. White crystals, mp 122–125 °C (EtOAc/hexane; 1/1); yield: 8.3 g (71%);  $[\alpha]_{\text{D}}^{20} +16.6$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm): (two rotamers)  $\delta$  1.39–1.50 (m, 9 H,  $\text{C}(\text{CH}_3)_3$ ), 3.08–3.25 (m, 2H,  $H(4a)$  +  $H(4b)$ ), 4.42–4.51 (m, 1H), 4.65–4.74 (m, 1.5H), 5.10–5.13 (m, 0.5H), 7.07–7.25 (m, 4H, *Ar*), 10.42 (brs, 1H,  $\text{CO}_2\text{H}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm):  $\delta$  28.2, 28.3, 30.8, 31.3, 43.8, 44.4, 52.3, 54.1, 81.0, 126.2, 126.3, 126.7, 126.9, 127.7, 128.5, 131.6, 131.8, 132.6, 133.7, 154.7, 155.6, 177.0, 177.7. Anal. Calcd for  $\text{C}_{15}\text{H}_{19}\text{NO}_4$  (277.3): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.89; H, 6.91; N, 4.97.

### General methods for preparation of Boc-protected substituted (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamides (1a-g).

**Method A.** To a solution of (*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (3.1 mmol),  $\text{Et}_3\text{N}$  (1 mL) in THF (25 mL) was added a solution of ethyl chloroformate (3.1 mmol) in THF (2 mL) during 10 min. After that, the appropriate amine (4 mmol) was added and the mixture was stirred at the temperature of 25 °C for 16 h. Then  $\text{Et}_3\text{N}\cdot\text{HCl}$  was filtered off and the filtrate was evaporated. The residue was dissolved in  $\text{CHCl}_3$  (30 mL) and washed with water ( $1 \times 10$  mL), aqueous solution of NaOH (5%) ( $1 \times 10$  mL), brine ( $1 \times 10$  mL), water ( $1 \times 10$  mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The organic phase was evaporated and the residue was recrystallized.

**Method B.** To a solution of (*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2.8 mmol), dicyclohexylcarbodiimide (3.1 mmol) and 4-dimethylaminopyridine (5 mg) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added a solution of appropriate amine (2.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at the temperature of 25 °C. The *N,N'*-dicyclohexylurea formed was filtered off after 5 h. The filtrate was concentrated and purified through chromatography column ( $\text{SiO}_2$ , EtOAc). The crude product was recrystallized.



**(S)-2-(tert-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1a):** Method A; white crystals; mp 130–131 °C (EtOAc/hexane; 1/1); yield: 780 mg (78%);  $[\alpha]_{\text{D}}^{20}$  –28.5 (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.42 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.05–3.08 (m, 2H, *H*(4a) + *H*(4b)), 4.40–4.61 (m, 3H, *H*(1a) + *H*(1b) + *H*(3)), 6.84 (brs, 2H, CONH<sub>2</sub>), 7.15 (s, 4H, *Ar*).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  28.0, 28.1, 31.5, 31.8, 43.9, 44.6, 52.9, 54.7, 79.2, 79.3, 125.9, 126.3, 126.7, 127.5, 128.1, 132.7, 133.5, 133.6, 134.6, 154.3, 154.7, 172.8, 173.3. Anal. Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> (276.3): C, 65.20; H, 7.30; N, 10.13. Found: C, 65.09; H, 7.31; N, 10.11.

**(S)-N-Phenyl-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1b):** Method A; white crystals; mp 150–152 °C (EtOAc/hexane; 1/1); yield: 780 mg (61%);  $[\alpha]_{\text{D}}^{20}$  –68.5 (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.38 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.05–3.10 (m, 1H, *H*(4a)), 3.21 (dd, 1H, *H*(4b),  $^2J = 15.5$  Hz,  $^3J = 6.2$  Hz), 4.47–4.51 (m, 1H, *H*(1a)), 4.64–4.68 (m, 2H, *H*(1b) + *H*(3)), 6.99–7.03 (m, 1H, *Ar*), 7.15–7.21 (m, 4H, *Ar*), 7.23–7.27 (m, 2H, *Ar*), 7.50–7.52 (m, 2H, *Ar*), 9.69 (s, 1H, CONH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  27.8, 28.0, 31.8, 44.0, 44.9, 53.9, 56.0, 79.2, 79.4, 119.1, 123.1, 125.7, 126.4, 126.5, 127.0, 127.1, 127.7, 128.6, 132.3, 133.8, 134.0, 135.3, 138.9, 154.0, 154.5, 170.1, 170.6. Anal. Calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> (352.4): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.78; H, 6.82; N, 8.05.

**(S)-N-(Pyridine-2-yl)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1c):** Method B; white crystals; mp 130–132 °C (cyclohexane); yield: 830 mg (65%);  $[\alpha]_{\text{D}}^{20}$  –65.1 (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.38 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.07–3.12 (m, 1H, *H*(4a)), 3.19–3.25 (m, 1H, *H*(4b)), 4.50–4.53 (m, 1H, *H*(1a)), 4.64–4.68 (m, 1H, *H*(1b)), 4.80 (brs, 1H, *H*(3)), 7.03–7.06 (m, 1H, *Py*), 7.19 (s, 4H, *Ar*), 7.68–7.72 (m, 1H, *Py*), 7.93–7.95 (m, 1H, *Py*), 8.28–8.29 (m, 1H, *Py*), 10.17 (s, 1H, CONH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  27.8, 28.0, 31.8, 44.0, 44.9, 53.8, 55.6, 79.2, 79.5, 113.2, 113.3, 119.3, 125.6, 125.8, 126.4, 126.6, 127.0, 127.1, 127.7, 132.3, 133.6, 134.0, 135.2, 138.0, 138.1, 147.9, 151.8, 151.9, 154.0, 154.6, 171.0, 171.5. Anal. Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub> (353.4): C, 67.97; H, 6.56; N, 11.89. Found: C, 68.26; H, 6.64; N, 11.81.

**(S)-N-Benzyl-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1d):** Method B; white crystals; mp 98–101 °C (EtOAc/hexane; 1/1); yield: 850 mg (65%);  $[\alpha]_{\text{D}}^{20}$  –17.5 (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.40 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.09 (m, 2H, *H*(1a) + *H*(1b)), 4.20 (d, 2H, CH<sub>2</sub>Ph,  $^3J = 5.95$  Hz), 4.46–4.63 (m, 3H, *H*(4a) + *H*(4b) + *H*(3)), 7.01 (m, 2H, *Ar*), 7.14–7.21 (m, 7H, *Ar*), 8.05 (brs, 1H, NH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  22.0, 22.3, 28.0, 28.2, 32.3, 44.4, 47.6, 55.0, 55.1, 79.2, 125.8, 125.9, 126.2, 126.5, 128.1, 133.6, 134.9, 144.3, 154.4, 170.6. Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> (366.5): C, 72.11; H, 7.15; N, 7.64. Found: C, 72.12; H, 6.86; N, 7.89.

**(S)-N-[(4-Methylphenyl)sulfonyl]-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1e):** Method B; white crystals; mp 98–101 °C (column chromatography; SiO<sub>2</sub>; EtOAc); yield: 900

mg (75%);  $[\alpha]_{\text{D}}^{20} +14.9$  (*c* 1.1, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  1.12–1.42 (m, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.36–2.38 (m, 3H, CH<sub>3</sub>), 2.83–2.97 (m, 1H, *H*(4*a*)), 3.08–3.17 (m, 1H, *H*(4*b*)), 4.35–4.65 (m, 3H, *H*(1*a*) + *H*(1*b*) + *H*(3)) 7.02–7.19 (m, 4H, *Ar*), 7.30–7.41 (m, 2H, *Ar*), 7.64–7.80 (m, 2H, *Ar*), 12.28 (s, 1H, *NH*).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  21.1, 27.6, 28.1, 31.1, 44.0, 44.9, 54.0, 55.3, 79.5, 79.9, 125.9, 126.6, 126.8, 127.1, 127.3, 127.7, 129.5, 129.6, 131.7, 132.6, 133.8, 134.9, 136.3, 144.1, 144.4, 153.8, 154.4, 170.4, 170.7. Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S (430.5): C, 61.38; H, 6.09; N, 6.51; S, 7.45. Found: C, 61.46; H, 6.02; N, 6.54; S, 7.40.

**(*S*)-*N*-[(1*R*)-1-Phenylethyl]-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide**

**(1f)**: Method A; white crystals; mp 137–139 °C (EtOAc/hexane; 1/1); yield: 1.8 g (64%);  $[\alpha]_{\text{D}}^{20} -77.5$  (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.27 (d, 3H, CH<sub>3</sub>,  $^3J = 7.41$  Hz), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.02–3.13 (m, 2H, *H*(1*a*) + *H*(1*b*)), 4.41–4.45 (m, 1H, *H*(3)), 4.54–4.58 (m, 2H, *H*(4*a*) + *H*(4*b*)), 4.84 (q, 1H, CH<sub>3</sub>CHPh,  $^3J = 7.41$  Hz), 7.15–7.25 (m, 9H, *Ar*), 7.82 (d, 1H, *NH*,  $^3J = 7.42$  Hz).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  22.0, 22.2, 27.9, 28.0, 31.8, 32.0, 44.0, 47.4, 53.1, 55.0, 79.0, 79.2, 125.4, 125.7, 125.8, 126.3, 126.4, 126.7, 127.2, 128.0, 132.5, 133.7, 133.8, 135.0, 144.4, 154.2, 154.6, 169.9, 170.4. Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> (380.5): C, 72.60; H, 7.42; N, 7.36. Found: C, 72.75; H, 7.51; N, 7.20.

**(*S*)-*N*-[(1*S*)-1-Phenylethyl]-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide**

**(1g)**: Method A; white crystals; mp 138–140 °C (EtOAc/hexane; 1/1); yield: 1.6 g (59%);  $[\alpha]_{\text{D}}^{20} +36.8$  (*c* 1.0, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.27–1.43 (m, 12H, C(CH<sub>3</sub>)<sub>3</sub> + CH<sub>3</sub>), 3.02–3.13 (m, 2H, *H*(4*a*) + *H*(4*b*)), 4.45–4.56 (m, 3H, *H*(1*a*) + *H*(1*b*) + *H*(3)), 4.79–4.87 (q, 1H, CH<sub>3</sub>CHPh,  $^3J = 7.05$  Hz), 7.07–7.09 (m, 2H, *Ar*), 7.13–7.23 (m, 7H, *Ar*), 7.77 (d, 1H, *NH*,  $^3J = 6.69$  Hz).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 25 °C): (two rotamers)  $\delta$  21.9, 22.1, 27.9, 28.1, 31.8, 32.2, 44.3, 44.9, 47.5, 53.6, 55.0, 79.0, 79.4, 125.7, 125.8, 126.0, 126.3, 126.6, 126.8, 127.3, 127.9, 133.1, 133.5, 134.0, 134.8, 144.2, 154.3, 154.6, 170.1, 170.5. Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> (380.5): C, 72.60; H, 7.42; N, 7.36. Found: C, 72.85; H, 7.46; N, 7.23.

**General method for preparation of thioamides 1h, 1i.**

The mixture of the corresponding amide **1f** or **1g** (1.3 mmol), Lawesson reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione; 283 mg; 0.7 mmol) in dry toluene (20 mL) was heated at the temperature of 110 °C for 6 h and then evaporated. The residue was purified through chromatography column (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) and the solid residue was recrystallized from EtOAc/hexane (1/1).

**(*S*)-*N*-[(1*R*)-1-Phenylethyl]-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-thiocarboxamide (1h)**

**(1h)**: Yellow oil, yield: 260 mg (50%);  $[\alpha]_{\text{D}}^{20} -71.5$  (*c* 3.1, MeOH).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, ppm, 75 °C):  $\delta$  1.29 (d, 3H, CH<sub>3</sub>,  $^3J = 7.29$  Hz), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.14–3.21 (m, 2H, *H*(1*a*) + *H*(1*b*)), 4.48–4.59 (m, 2H, *H*(4*a*) + *H*(4*b*)), 4.81 (t, 1H, *H*(3),  $^3J = 6.29$  Hz), 5.61 (q, 1H, CH<sub>3</sub>CHPh,  $^3J = 7.29$  Hz),

7.13–7.31 (m, 9H, *Ar*), 9.56 (brs, 1H, *NH*).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm, 75 °C):  $\delta$  20.1, 20.4, 27.8, 28.1, 34.7, 35.1, 44.7, 45.6, 53.1, 61.4, 62.4, 79.4, 79.6, 126.1, 126.3, 126.6, 126.8, 127.0, 127.2, 127.2, 128.3, 128.4, 134.3, 135.9, 142.3, 154.2, 154.5, 171.0, 202.4, 203.1. Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$  (380.5): C, 69.66; H, 7.12; N, 7.06; S, 8.09. Found: C, 69.75; H, 7.00; N, 7.14; S, 8.03.

**(*S*)-*N*-[(1*S*)-1-Phenylethyl]-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-thiocarboxamide (**1i**):** Pale yellow crystals, mp 110–112 °C; yield: 270 mg (52%);  $[\alpha]_{\text{D}}^{20}$   $-1.9$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR (DMSO- $d_6$ , ppm, 75 °C):  $\delta$  1.36 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.46 (d, 3H,  $\text{CH}_3$ ,  $^3J = 7.05$  Hz), 3.19–3.30 (m, 2H,  $H(1a) + H(1b)$ ), 4.51–4.61 (m, 2H,  $H(4a) + H(4b)$ ), 4.85 (t, 1H,  $H(3)$ ,  $^3J = 6.04$  Hz), 5.57 (q, 1H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 7.05$  Hz), 6.96–6.98 (m, 2H, *Ar*), 7.14–7.28 (m, 7H, *Ar*), 9.58 (d, 1H, *NH*,  $^3J = 7.05$  Hz).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm, 25 °C): (two rotamers)  $\delta$  19.9, 28.0, 35.1, 44.8, 53.2, 62.7, 79.3, 99.6, 126.1, 126.6, 127.3, 128.1, 134.2, 135.7, 141.9, 154.2, 202.6. Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$  (380.5): C, 69.66; H, 7.12; N, 7.06; S, 8.09. Found: C, 69.71; H, 7.05; N, 7.11; S, 8.01.

#### General method for deprotection of *N*-Boc intermediates.

The solution of *N*-Boc protected amides (**1a–g**) and thioamides (**1h, i**) was kept in trifluoroacetic acid (2 mL) at the temperature of 0 °C for 2 h. The residue obtained after evaporation of trifluoroacetic acid was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL). In the case of amides **1a–g**, the organic phase was washed with water (1  $\times$  20 mL), aqueous solution of NaOH (5%; 1  $\times$  20 mL), saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (1  $\times$  20 mL) and water (1  $\times$  20 mL). In the case of thioamides **1h, i**, the organic phase was mixed with dry  $\text{Et}_3\text{N}$  (1  $\times$  10 mL) and the formed salt was filtered off. After evaporation, the crude amides and thioamides were purified by flash column chromatography ( $\text{SiO}_2$ ; EtOAc) and recrystallized.

**(*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxamide (**2a**):** From **1a** (700 mg; 2 mmol); white crystals; mp 159–162 °C (EtOAc/hexane; 1/1); yield: 490 mg (70%);  $[\alpha]_{\text{D}}^{20}$   $-31.5$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.76 (brs, 1H, *NH*), 2.87 (dd, 1H,  $H(4a)$ ,  $^2J = 16.28$  Hz,  $^3J = 10.51$  Hz), 3.24 (dd, 1H,  $H(4b)$ ,  $^2J = 16.28$  Hz,  $^3J = 5.03$  Hz), 3.59 (dd, 1H,  $H(3)$ ,  $^3J = 5.03$  Hz,  $^3J = 10.51$  Hz), 3.99–4.08 (m, 2H,  $H(1a) + H(1b)$ ), 5.53 (brs, 1H,  $\text{CONH}_2$ ), 7.00–7.15 (m, 2H,  $\text{CONH}_2 + \text{Ar}$ ), 7.17–7.18 (m, 3H, *Ar*).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  29.7, 30.8, 47.7, 56.5, 125.6, 126.3, 126.6, 129.3, 134.1, 135.7, 176.0. Anal. Calcd for  $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$  (176.2): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.25; H, 6.77; N, 15.92.

**(*S*)-*N*-Phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**2b**):** From **1b** (570 mg; 1.5 mmol); white crystals; mp 166–167 °C (EtOAc/hexane; 1/1); yield: 490 mg (70%);  $[\alpha]_{\text{D}}^{20}$   $-86.0$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.72 (brs, 1H, *NH*), 2.87 (dd, 1H,  $H(4a)$ ,  $^2J = 16.44$  Hz,  $^3J = 10.64$  Hz), 3.30 (dd, 1H,  $H(4b)$ ,  $^2J = 16.44$  Hz,  $^3J = 5.16$  Hz), 3.62 (dd, 1H,  $H(3)$ ,  $^3J = 5.16$  Hz,  $^3J = 10.64$  Hz), 3.96–4.05 (m, 2H,  $H(1a) + H(1b)$ ), 7.04–7.10 (m, 2H, *Ar*), 7.14–7.20 (m, 3H, *Ar*), 7.31 (t, 2H, *Ar*,  $^3J = 7.26$  Hz), 7.60 (d, 2H, *Ar*,  $^3J = 7.26$  Hz), 9.31 (brs, 1H, *CONH*).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  30.4,

47.4, 56.7, 119.3, 124.0, 125.4, 126.7, 128.9, 129.1, 134.3, 136.0, 137.6, 171.2. Anal. Calcd for  $C_{15}H_{26}N_2O$  (252.3): C, 76.16; H, 6.39; N, 11.10. Found: C, 75.92; H, 6.69; N, 11.19.

**(S)-N-(Pyridine-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2c):** From **1c** (300 mg; 0.8 mmol); white crystals; mp 108–109 °C (EtOAc/hexane; 1/1); yield: 490 mg (71%);  $[\alpha]_D^{20}$  –59.4 (*c* 1.0, MeOH).  $^1H$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  1.83 (brs, 1H, *NH*), 2.89 (dd, 1H, *H(4a)*,  $^2J = 16.06$  Hz,  $^3J = 10.29$  Hz), 3.28 (dd, 1H, *H(4b)*,  $^2J = 16.06$  Hz,  $^3J = 5.33$  Hz), 3.66 (dd, 1H, *H(3)*,  $^3J = 5.33$  Hz,  $^3J = 10.29$  Hz), 3.96–4.04 (m, 2H, *H(1a) + H(1b)*), 6.99–7.06 (m, 2H, *Ar*), 7.14–7.17 (m, 3H, *Ar*), 7.64–7.68 (m, 1H, *Ar*), 8.23–8.27 (m, 2H, *Ar*), 9.88 (brs, 1H, *CONH*).  $^{13}C$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  30.5, 47.4, 56.8, 113.4, 119.9, 125.7, 126.5, 126.8, 129.2, 134.3, 136.4, 138.4, 148.1, 151.2, 172.2. Anal. Calcd for  $C_{15}H_{15}N_3O$  (253.3): C, 71.13; H, 5.97; N, 16.59. Found: C, 70.87; H, 5.84; N, 16.36.

**(S)-N-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2d):** From **1d** (600 mg; 1.6 mmol); white crystals; mp 103–105 °C (EtOAc/hexane; 1/1); yield: 320 mg (73%);  $[\alpha]_D^{20}$  –79.2 (*c* 1.0, MeOH).  $^1H$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  1.66 (brs, 1H, *NH*), 2.88 (dd, 1H, *H(4a)*,  $^2J = 16.22$  Hz,  $^3J = 10.30$  Hz), 3.27 (dd, 1H, *H(4b)*,  $^2J = 16.22$  Hz,  $^3J = 4.99$  Hz), 3.61 (dd, 1H, *H(3)*,  $^3J = 4.99$  Hz,  $^3J = 10.30$  Hz), 3.93–4.02 (m, 2H, *H(1a) + H(1b)*), 4.42–4.52 (m, 2H,  $CH_2Ph$ ), 7.03–7.05 (m, 1H, *Ar*), 7.14–7.21 (m, 3H, *Ar*), 7.23–7.35 (m, 5H, *Ar*), 7.58 (brs, 1H, *CONH*).  $^{13}C$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  31.0, 43.1, 47.5, 56.4, 125.5, 126.6, 127.7, 128.6, 129.2, 134.4, 136.0, 138.3, 173.0. Anal. Calcd for  $C_{15}H_{18}N_2O$  (266.34): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.51; H, 6.80; N, 10.41.

**(S)-N-[(4-Methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2e):** From **1e** (300 mg; 0.7 mmol); yellowish oil; yield: 320 mg (74%);  $[\alpha]_D^{20}$  –55.7 (*c* 1.0, MeOH).  $^1H$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  2.28 (s, 3H,  $CH_3$ ), 3.07–3.23 (m, 2H, *H(4a) + H(4b)*), 4.02–4.05 (m, 1H, *H(3)*), 4.24–4.28 (m, 1H, *H(1a)*), 4.40–4.44 (m, 1H, *H(1b)*), 6.98–7.06 (m, 4H, *Ar*), 7.16–7.26 (m, 2H, *Ar*), 7.32–7.50 (m, 2H, *Ar*), 8.34 (brs, 1H, *NH*).  $^{13}C$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  21.4, 29.7, 30.3, 45.0, 57.3, 126.3, 126.5, 127.0, 127.8, 128.5, 128.7, 129.0, 131.9, 139.8, 141.8, 173.5. Anal. Calcd for  $C_{17}H_{18}N_2O_3S$  (330.40): C, 61.80; H, 5.49; N, 8.48; S, 9.70. Found: C, 61.61; H, 5.91; N, 7.95; S, 9.79.

**(S)-N-[(1R)-1-Phenylethyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2f):** From **1f** (600 mg; 1.6 mmol); white crystals; mp 124–126 °C (EtOAc/hexane; 1/1); yield: 300 mg (69%);  $[\alpha]_D^{20}$  –118.0 (*c* 1.0, MeOH).  $^1H$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  1.49 (d, 3H,  $CH_3$ ,  $^3J = 6.78$  Hz), 1.68 (brs, 1H, *NH*), 2.86 (dd, 1H, *H(4a)*,  $^2J = 16.32$  Hz,  $^3J = 10.56$  Hz), 3.24 (dd, 1H, *H(4b)*,  $^2J = 16.53$  Hz,  $^3J = 5.01$  Hz), 3.53 (dd, 1H, *H(3)*,  $^3J = 5.01$  Hz,  $^3J = 10.56$  Hz), 4.00 (s, 2H, *H(1a) + H(1b)*), 5.14 (q, 1H,  $CH_3CHPh$ ,  $^3J = 7.28$  Hz), 7.04–7.05 (m, 1H, *Ar*), 7.14–7.20 (m, 3H, *Ar*), 7.26–7.29 (m, 1H, *Ar*), 7.33–7.37 (m, 4H, *Ar*), 7.46 (d, 1H, *CONH*,  $^3J = 7.50$  Hz).  $^{13}C$  NMR ( $CDCl_3$ , ppm, 25 °C):  $\delta$  22.0, 26.9, 31.0, 47.6, 48.3, 56.5, 125.6, 126.2, 126.6, 127.3, 128.6, 129.2, 134.3, 135.8, 143.3, 172.3. Anal. Calcd for  $C_{18}H_{20}N_2O$  (280.4): C, 77.11; H, 7.19; N, 9.99. Found: C, 76.92; H, 7.18; N, 9.72.

**(S)-N-[(1S)-1-Phenylethyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2g):** From **1g** (570 mg; 1.5 mmol); white crystals; mp 124–126 °C (EtOAc/hexane; 1/1); yield: 290 mg (68%);  $[\alpha]_{\text{D}}^{20} +42.2$  (*c* 1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.50 (d, 3H,  $\text{CH}_3$ ,  $^3J = 6.61$  Hz), 1.64 (brs, 1H,  $\text{NH}$ ), 2.79 (dd, 1H,  $H(4a)$ ,  $^2J = 16.53$  Hz,  $^3J = 9.92$  Hz), 3.31 (dd, 1H,  $H(4b)$ ,  $^2J = 16.53$  Hz,  $^3J = 4.41$  Hz), 3.57 (dd, 1H,  $H(3)$ ,  $^3J = 4.41$  Hz,  $^3J = 9.92$  Hz), 3.92–4.02 (m, 2H,  $H(1a) + H(1b)$ ), 5.13 (q, 1H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 7.05$  Hz), 7.02–7.04 (m, 1H, *Ar*), 7.11–7.18 (m, 3H, *Ar*), 7.22–7.24 (m, 3H, *Ar*), 7.28–7.32 (m, 2H, *Ar*), 7.52 (d, 1H,  $\text{CONH}$ ,  $^3J = 8.03$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  22.0, 30.1, 47.5, 48.1, 56.4, 125.5, 155.9, 126.1, 127.1, 128.6, 129.1, 134.4, 135.9, 143.3, 172.1. Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$  (280.4): C, 77.11; H, 7.19; N, 9.99. Found: C, 76.98; H, 7.11; N, 9.78.

**(S)-N-[(1R)-1-Phenylethyl]-1,2,3,4-tetrahydroisoquinoline-3-thiocarboxamide (2h):** From **1h** (270 mg; 0.7 mmol); yellow oil; yield: 160 mg (77%);  $[\alpha]_{\text{D}}^{20} -119.9$  (*c* 2.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.49 (d, 3H,  $\text{CH}_3$ ,  $^3J = 7.03$  Hz), 1.71 (s, 1H,  $\text{NH}$ ), 2.85 (dd, 1H,  $H(4a)$ ,  $^2J = 15.79$  Hz,  $^3J = 9.81$  Hz), 3.49 (dd, 1H,  $H(4b)$ ,  $^2J = 15.79$  Hz,  $^3J = 5.28$  Hz), 3.79 (dd, 1H,  $H(3)$ ,  $^3J = 5.28$  Hz,  $^3J = 9.81$  Hz), 3.83–3.94 (m, 2H,  $H(1a) + H(1b)$ ), 5.71 (q, 1H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 6.90$  Hz), 7.02–7.04 (m, 1H, *Ar*), 7.11–7.18 (m, 3H, *Ar*), 7.23–7.29 (m, 1H, *Ar*), 7.30–7.35 (m, 4H, *Ar*), 9.72 (d, 1H,  $\text{CSNH}$ ,  $^3J = 6.27$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  20.2, 34.5, 46.6, 53.1, 62.6, 125.1, 126.1, 126.2, 126.6, 127.5, 128.4, 128.5, 134.6, 136.1, 141.2, 202.2. Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}$  (296.4): C, 72.93; H, 6.80; N, 9.45; S, 10.82. Found: C, 72.99; H, 6.73; N, 9.53; S, 10.74.

**(S)-N-[(1S)-1-Phenylethyl]-1,2,3,4-tetrahydroisoquinoline-3-thiocarboxamide (2i):** From **1i** (700 mg; 1.8 mmol); white crystals, mp 110–112 °C (propan-2-ol/hexane, 2/1); yield: 370 mg (69%);  $[\alpha]_{\text{D}}^{20} +28.0$  (*c* 1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.59 (d, 3H,  $\text{CH}_3$ ,  $^3J = 6.75$  Hz), 1.76 (brs, 1H,  $\text{NH}$ ), 2.93 (dd, 1H,  $H(4a)$ ,  $^3J = 9.03$  Hz,  $^2J = 15.76$  Hz), 3.52 (dd, 1H,  $H(4b)$ ,  $^2J = 15.76$  Hz,  $^3J = 5.75$  Hz), 3.89–4.03 (m, 3H,  $H(1a) + H(1b) + H(3)$ ), 5.71 (q, 1H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 7.06$  Hz), 7.07–7.11 (m, 3H, *Ar*), 7.16–7.22 (m, 3H, *Ar*), 7.24–7.30 (m, 3H, *Ar*), 9.81 (brs, 1H,  $\text{CSNH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  20.4, 34.5, 46.7, 53.1, 52.6, 125.3, 126.1, 126.3, 127.3, 126.6, 134.8, 136.2, 141.5, 202.5. Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}$  (296.4): C, 72.93; H, 6.80; N, 9.45; S, 10.82. Found: C, 72.81; H, 6.79; N, 9.35; S, 10.72.

#### Preparation of cyclic compounds **3a**, **3b**.

**(5S)-3(4-Nitrophenyl)-2-[(1R)-1-phenylethyl]-2,3,10,10a-tetrahydro-5H-imidazo[1,5-b]isoquinoline-1-thione (3a).** Compound **3a** was prepared by reaction of compound **2i** (30 mg; 0.1 mmol) with 4-nitrobenzaldehyde (16.5 mg; 0.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) in the presence of molecular sieve 4Å for a reaction period of 3 days. Then the reaction mixture was evaporated, and the product was obtained by column chromatography ( $\text{SiO}_2$ , EtOAc/petroleum ether, 1/2). Yield: 28.6 mg (66%), mp 82–83 °C;  $[\alpha]_{\text{D}}^{20} -31.9$  (*c* 1.0, MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.56 (d, 3H,  $\text{CH}_3$ ,  $^3J = 6.54$  Hz), 1.23 (dd, 1H,  $^2J$

= 11.75 Hz,  $^2J = 16.72$  Hz), 3.45–3.54 (m, 3H), 3.84 (d, 1H,  $^2J = 14.54$  Hz), 4.25 (q, 1H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 6.54$  Hz), 5.10 (s, 1H), 6.91–6.93 (m, 1H, *Ar*), 7.11–7.15 (1H, *Ar*), 7.18–7.21 (m, 1H, *Ar*), 7.23–7.27 (m, 2H, *Ar*), 7.32–7.36 (m, 2H, *Ar*), 7.39–7.41 (m, 2H, *Ar*), 7.74–7.77 (m, 2H, *Ar*), 8.23–8.25 (m, 2H, *Ar*).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  24.0, 34.0, 53.6, 66.8, 67.1, 73.5, 124.1, 126.2, 126.4, 126.8, 126.9, 127.1, 128.5, 129.3, 129.4, 144.3, 145.0, 148.4, 165.5. Anal. Calcd for  $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$  (429.5): C, 69.91; H, 5.45; N, 9.78; S, 7.47. Found: C, 69.75; H, 5.38; N, 9.69; S, 7.41.

**(5S)-3,3-Dimethyl-2-[(1R)-1-phenylethyl]-2,3,10,10a-tetrahydro-5H-imidazo[1,5-b]isoquinoline-1-thione (3b).** Compound **3b** was prepared by reaction of compound **2i** (30 mg; 0.1 mmol) with acetone (1 mL; 13 mmol) for a reaction period of 7 days. Then the mixture was evaporated to provide the crude product in almost quantitative yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm, 25 °C):  $\delta$  1.19 (s, 3H,  $\text{CH}_3$ ), 1.26 (s, 1H), 1.45 (s, 3H,  $\text{CH}_3$ ), 1.92 (q, 3H,  $\text{CH}_3\text{CHPh}$ ,  $^3J = 7.50$  Hz), 2.63 (s, 1H), 3.03 (dd, 1H,  $^3J = 10.70$  Hz,  $^2J = 15.75$  Hz), 3.45 (dd, 1H,  $^3J = 4.19$  Hz,  $^2J = 16.19$  Hz), 3.68 (dd, 1H,  $^3J = 4.34$  Hz,  $^2J = 11.13$  Hz), 3.84 (s, 1H), 7.06–7.38 (m, 9H, *Ar*). Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{S}$  (336.5): C, 74.96; H, 7.19; N, 8.33; S, 9.53. Found: C, 74.82; H, 6.96; N, 8.54; S, 9.61.

#### Asymmetric Aldol reaction.

To a solution of 4-nitrobenzaldehyde (30 mg; 0.2 mmol) in acetone or aqueous acetone (2 mL), catalyst **2a-i** was added (0.04 mmol) and the resulting mixture was stirred at the temperature of 25 °C or –10 °C for a time period of 7 days. The residue formed after evaporation of the solvent was analyzed by  $^1\text{H}$  NMR. The crude product was purified by column chromatography ( $\text{SiO}_2$ , EtOAc), and the product obtained was analyzed by HPLC. Daicel Chiralpak AS-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH 70:30; flow rate 0.5 mL  $\text{min}^{-1}$ ;  $\lambda = 254$  nm;  $t_R$  (*R*) = 25.53 min;  $t_R$  (*S*) = 33.42 min.

#### Crystallographic data for compound 2h.

The single crystals of **2h** suitable for X-ray diffraction were obtained by slow evaporation from saturated solution in EtOAc/*n*-hexane. The X-Ray data for light yellow crystals were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with Mo  $\text{K}_\alpha$  radiation ( $\lambda = 0.71073$  Å), a graphite monochromator, and the  $\phi$  and  $\chi$  scan mode. Data reductions were performed with DENZO-SMN.<sup>19</sup> The absorption was corrected by integration methods.<sup>20</sup> Structures were solved by direct methods (Sir92)<sup>21</sup> and refined by full matrix least-square based on  $F^2$  (SHELXL97).<sup>22</sup> Hydrogen atoms were mostly localized on a difference Fourier map, however to ensure uniformity of treatment of crystal, all hydrogen were recalculated into idealized positions (riding model) and assigned temperature factors  $\text{H}_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}$  (pivot atom) or of  $1.5U_{\text{eq}}$  (methyl). H atoms in methyl, methylene, methine moieties and hydrogen atoms in aromatic rings were placed with C–H distances of 0.96, 0.97, 0.98 and 0.93 Å and H atoms for N–H were assigned according to maxima on the electron density difference

Fourier map.  $R_{\text{int}} = \sum |F_o^2 - F_{o,\text{mean}}^2| / \sum F_o^2$ ,  $\text{GOF} = [\sum (w(F_o^2 - F_c^2)^2) / (N_{\text{diffrs}} - N_{\text{params}})]^{1/2}$  for all data,  $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$  for observed data,  $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$  for all data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC# **1001485**). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Crystallographic data:  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}$ ,  $M = 296.42$ ,  $a = 5.8660(4)$ ,  $b = 8.6230(7)$ ,  $c = 31.1701(18)$  Å,  $\alpha = \beta = \gamma = 90^\circ$ ,  $Z = 4$ ,  $V = 1576.66(19)$  Å<sup>3</sup>,  $D_c = 1.249$  g.cm<sup>-3</sup>,  $\mu = 0.201$  mm<sup>-1</sup>,  $T_{\text{min}}/T_{\text{max}} = 0.963/0.984$ ;  $-6 \leq h \leq 7$ ,  $-10 \leq k \leq 11$ ,  $-32 \leq l \leq 40$ ; 7205 reflections measured ( $\theta_{\text{max}} = 27.5^\circ$ ), 7164 independent ( $R_{\text{int}} = 0.0463$ ), 2888 with  $I > 2\sigma(I)$ , 190 parameters,  $S = 1.160$ ,  $RI(\text{obs. data}) = 0.0480$ ,  $wR2(\text{all data}) = 0.0886$ ; max., min. residual electron density = 0.240,  $-0.286$  eÅ<sup>-3</sup>. The compound **2h** crystallizes in the orthorhombic chiral space group  $P2_12_12_1$  with 4 molecules within the crystal lattice. The supramolecular architecture of the molecule consists of infinite chains where the molecules are interconnected by N–H···S short contacts. The values found for interatomic distances and angles are within the typical range for single and double bonds, respectively,<sup>23</sup> and also comparable to similar structures of appropriate compounds reported elsewhere.<sup>24</sup>

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