Synthesis of (*R*)- and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamides and (*R*)- and (*S*)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines

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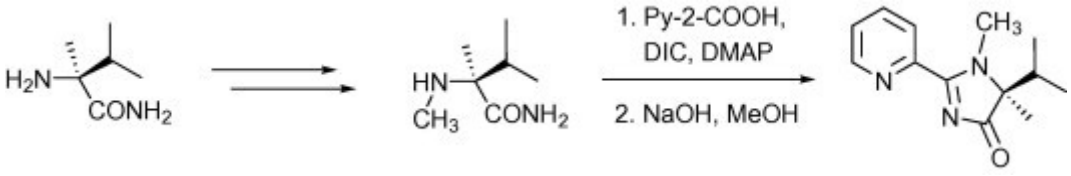
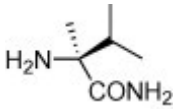
Abstract

Both (*R*)- and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamides have been prepared by the reductive benzylation of (*R*)- and (*S*)-2-amino-2,3-dimethylbutanamides, followed by reductive methylation and hydrogenolytic removal of the benzyl group. The reductive benzylation is chemoselective, and not accompanied by dibenzylation even with the application of excess benzaldehyde. Acylation of the (*R*)- and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamides with picolinic acid and subsequent ring closure gave the respective (*R*)- and (*S*)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines. Their complexes with Cu(I) catalyze the Kharash–Sosnovsky allylic oxidation with overall yields as high as 99% but with low enantioselectivity.

Graphical abstract





(*S*)-2-Amino-2,3-dimethylbutanamide

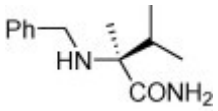
$C_6H_{14}N_2O$

Ee >99%

$[\alpha]_D^{20} = -56.0$ (*c* 1.03, THF)

Source of chirality: diastereoisomeric resolution

Absolute configuration: (*S*)



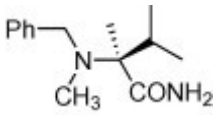
(*S*)-2-*N*-Benzylamino-2,3-dimethylbutanamide

Ee >99%

$[\alpha]_D^{20} = +16.7$ (*c* 0.41, THF)

Absolute configuration: (*S*)

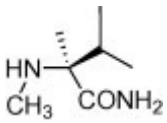
$C_{13}H_{20}N_2O$



(*S*)-2-*N*-Benzyl-*N*-methylamino-2,3-dimethylbutanamide

Ee >99%
$[\alpha]_D^{20} = +12.9$ (*c* 0.42, THF)
Absolute configuration: (*S*)

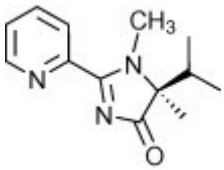
$C_{14}H_{22}N_2O$



(*S*)-2-*N*-Methylamino-2,3-dimethylbutanamide

Ee >99%
$[\alpha]_D^{20} = -14.2$ (*c* 0.48, THF)
Absolute configuration: (*S*)

$C_7H_{16}N_2O$



(*S*)-(5-Isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridine

Ee >99%
$[\alpha]_D^{20} = -68.0$ (*c* 0.51, THF)
Absolute configuration: (*S*)

$C_{13}H_{17}N_3O$

1. Introduction

The importance of new nitrogen heterocyclic compounds and their complexes with metal ions lies in their potential applicability as suitable catalysts in many chemical processes.[1] If, in addition, the complex involves a heterocyclic system containing in its structure a stereogenic centre, it can be used as a homogeneous or heterogeneous catalyst for asymmetric syntheses.[1] The 4,5-dihydro-1*H*-imidazol-5-ones prepared by us also belong among chiral nitrogen-containing ligands.[2] In our previous work, we found out that Rh(III) complexes of substituted 2,6-bis(4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridines exhibit excellent catalytic activity in the deallylation reactions of allylmalonates with various alkyl groups.[3] Analogous Fe(III) complexes catalyze the ring closure of substituted 2-chloro-1,6-dienes giving 1-methylidene-2-propylcyclopentanes.[4] Since the 4,5-dihydro-1*H*-imidazol-5-ones prepared contain a stereogenic centre, they were prepared in their enantiomerically pure forms, and their Cu(II) coordination compounds were tested as catalysts for the Henry reaction.[2b] and [2c]

In the 2,6-bis(4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridines **1** and 2-(4-isopropyl-1,4-dimethyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridines **2** that we originally prepared, the stereogenic centre is adjacent to the nitrogen atom participating in the coordination with a metal atom (the 4-position of 4,5-dihydro-1*H*-imidazole skeleton) (Fig. 1). Recently an example has been described where a relocation of the stereogenic centre in the ligand to a position more remote from the chelate-forming centre positively affected the enantioselectivity of a catalytic process.[5] In order to verify this possibility in the case of our ligands, the aim of the this work was to prepare enantiomerically pure (5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridine ligands **7**. These ligands differ from our earlier derivatives in having their stereogenic centre at the 5-position of the 4,5-dihydro-1*H*-imidazole cycle, that is, at a position more remote from the chelate-forming centre than that present in our earlier ligands.[1] and [2]

Another aim of this work was to compare the enantioselectivity of the newly suggested ligands with our earlier

derivatives using a suitable model asymmetric reaction. Since the synthesis of the newly suggested (*R*)- and (*S*)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines **7** unavoidably starts from (*R*)- and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamides **6**, it was crucial for this research to develop their synthesis. The procedure chosen needs a strategy entirely different from that used for the racemic 2-*N*-methylamino-2,3-dimethylbutanamides[6] and [7] (see Chart 1).

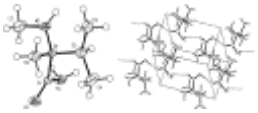


Figure 1. ORTEP representation and projection of crystal structure of compound (*R*)-(+)-**6**.

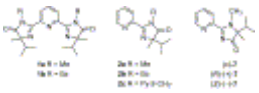


Chart 1. 4,5-Dihydro-1*H*-imidazol-5(4)-one chiral ligands.

2. Results and discussion

2.1. Synthesis of 2-*N*-methylamino-2,3-dimethylbutanamides 6

The enantiomerically pure (*R*)- and (*S*)-2-amino-2,3-dimethylbutanamides can be easily prepared by the partial hydrolysis of (*R*)- and (*S*)-2-amino-2,3-dimethylbutanenitriles, respectively; these were obtained by the resolution of their racemate with tartaric acid.[8] On the other hand, neither the resolution of racemate of 2-*N*-methylamino-2,3-dimethylbutanamide **6** nor that of 2-*N*-methylamino-2,3-dimethylbutanenitrile by means of chiral acids was successful. The strategy chosen for preparing compounds **7** consists of selective methylation of the amino group in the enantiomerically pure 2-amino-2,3-dimethylbutanamides, whereas direct methylation by alkylating agents, such as methyl iodide or dimethyl sulfate, may lead to the non-selective formation of mixtures of various methylated products. Also the direct Eschweiler–Clark methylation with formaldehyde in the presence of reducing agents (HCOOH, $NaBH_3CN$) is not appropriate, since it usually results in double methylation, producing the respective tertiary amine.[9] A chemoselective procedure for the monomethylation of primary amino groups was described for the esters of amino acids,[10] which involved the reduction of the corresponding imine of benzophenone, followed by reductive amination with formaldehyde and hydrogenolysis.[10] In our case, the first reductive amination of 2-amino-2,3-dimethylbutanamides, that is, by using the benzaldehyde/$NaBH_3CN$ system, was employed to prepare 2-*N*-methylamino-2,3-dimethylbutanamides **6**. We found that in this case, thanks to the lower reactivity but higher selectivity of the benzaldehyde as compared with formaldehyde, the Eschweiler–Clark reaction only produced monobenzyl derivatives. Monobenzylation was observed even in the presence of an excess of benzaldehyde (1.3 equiv); on the other hand, this excess proved to be favourable for achieving very good conversions (85–97%). Subsequently, the *N*-benzyl derivatives **4** were submitted to an analogous reaction with formaldehyde, to afford the racemic and enantiomerically pure (*R*)- and (*S*)-*N*-benzyl-*N*-methyl derivatives **5**, in $\geqslant$90% yields. The benzyl group in the latter product **5** was removed quantitatively by hydrogenolysis on palladium at a mild overpressure of hydrogen (ca. 5 kPa). This sequence was also used to prepare racemic 2-*N*-

methylamino-2,3-dimethylbutanamide and (*R*)- and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamides **6** in 75–80% overall yields (Scheme 1). The structure of compound (*R*)-(+)-**6**was confirmed by X-ray diffraction analysis.

Scheme 1.

The molecular arrangement of compound (*R*)-(+)-**6** presented in Figure 1 shows that individual molecules are interconnected by hydrogen bonds between the nitrogen atom of one of the amide groups and the oxygen atom of the next one. This leads to a double-layer structure of linearly connected molecules, the alkyl groups of the molecules in these two layers being oriented mutually against each other. This arrangement in the solid phase is very similar to the crystal structure of (*S*)- and (*rac*)-valine with an analogous type of double-layer arrangement.[11]

2.2. Synthesis of (5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines 7

The preparation of substituted 2-aryl-5-alkyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-one derivatives can be effected in two steps; 2-*N*-methylaminoalkanamide is treated with the corresponding aroyl chloride, and the resulting 2-*N*-benzoyl-2-*N*-methylaminoalkanamide is subsequently cyclized by a base.[2c] and [7] We expected that (*R*)- and (*S*)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines can be prepared in the same way, involving *N*-acylation with activated pyridine-2-carboxylic acid. Due to steric hindrance, 2-*N*-methylamino-2,3-dimethylbutanamides **6** are rather unreactive and can only be acylated with very reactive reagents. However, the requisite pyridine-2-carbonyl chloride is not available, and the previously described[2b] activation of pyridine-2-carboxylic acid by means of ethyl chloroformate proved to be unsuccessful in this case. Furthermore, the recently described *N*-acylation via aminolysis of methyl pyridine-2-carboxylate catalyzed by Lewis acids[12] also failed in our case. The best way for the acylation of aminoamides **6** with pyridine-2-carboxylic acid proved to be activation with *N*,*N*′-diisopropylcarbodiimide. However, the application of this procedure gave a mixture of acylation and ring-closure products **7**. Therefore, the acylation products were not isolated and the crude products immediately submitted to the base-catalyzed ring closure, giving rise to the cyclic products **7** (Scheme 1). However, the removal of *N*,*N*′-diisopropylurea, arising as a byproduct, proved to be a problem. Complete purification was achieved only after repeated recrystallization of compounds **7** from cyclohexane. In principle, this problem could be circumvented by using *N*-ethyl-*N*′-(γ-dimethylaminopropyl)carbodiimide, as the corresponding urea can easily be removed by extraction into water.[13] However, in our case the application of *N*-ethyl-*N*′-(γ-dimethylaminopropyl)carbodiimide prolonged the reaction time, owing to the rearrangement of the *O*-acylurea into its non-reactive *N*-acyl isomer (see Fig. 2).

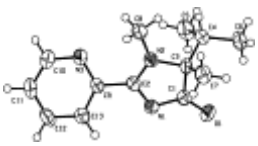


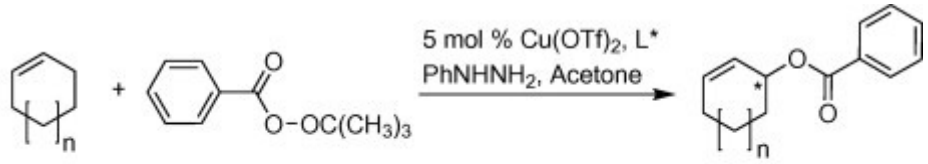
Figure 2. ORTEP representation of structure of compound (*R*)-(+)-**7**.

2.3. Asymmetric allylic oxidation catalyzed by Cu(I) complexes of 1, 2 and 7

The newly prepared chiral ligands **7** were tested for their catalytic activity in the allylic oxidation of olefins (Kharash–Sosnovsky reaction) and compared with the previously reported derivatives of 4,5-dihydro-1*H*-imidazol-5-ones (**1** and **2**).[2a], [2b] and [3] It is well known that this reaction is effectively catalyzed by Cu(I) complexes of nitrogen ligands.[14] The Cu(I) complexes of ligands **1**, **2** and **7** were prepared in situ by reducing the ligand/$Cu(OTf)_2$ complexes with phenylhydrazine. Five- to seven-membered cycloalkenes and *tert*-butyl peroxybenzoate oxidant were utilized. The reactions were performed in acetone, which has been generally accepted as the most appropriate solvent.[14h] The reaction times were in the order of days (1–42 days), which represents a distinct retardation as compared with the catalysis by analogous oxazoline derivatives.[14] With respect to this slow course of the reaction, it was impossible to carry out any more significant study of temperature effect upon enantioselectivity (reaction temperatures 0 and 20 °C). The very slow reaction course is probably caused by a substantial steric hindrance exhibited by the alkyl groups bound to the asymmetric centre. All the ligands studied **1**, **2** and **7** (Table 1) showed very low selectivity (0–22% ee). The results given in Table 1 indicate that ligand (*R*)-(+)-**7** is rather less enantioselective than analogous ligands with the chiral centre at 4-position (**1** and **2**). For instance, the oxidation product of cyclopentene **9a** was obtained with catalysis by ligand (*R*)-(+)-**7** in 9% ee (Table 1, entry 1), while the catalysis by ligands **1a** and **2a** gave 14% and 15% ee, respectively (Table 1, entries 3 and 13).

Table 1.

Asymmetric allylic oxidation of cycloalkenes **8a**–**c** catalyzed by Cu(I) complexes of chiral ligands **1**, **2** and **7**



8a, n = 0
8b, n = 1
8c, n = 2

9a, n = 0
9b, n = 1
9c, n = 2

Entry	Ligand	Olefin	Temp (°C)	Time (d)	Yield (%)	ee (%)
1	(*R*)-(+)-**7**	**8a**	20	8	56	9
2	(*R*)-(+)-**7**	**8b**	20	13	80	<3
3	**2a**	**8a**	20	2.5	99	15
4	**2a**	**8b**	20	7	50	13[a]
5	**2a**	**8c**	20	5	82	18[a]
6	**2a**	**8c**	0	24	58	18[a]
7	**2b**	**8a**	20	1	98	16
8	**2b**	**8a**	0	42	13	21
9	**2b**	**8b**	20	2	81	14[a]
10	**2b**	**8c**	20	2	65	17[a]
11	**2b**	**8c**	0	25	47	22[a]
12	**2c**	**8a**	20	31	10	<3
13	**1a**	**8a**	20	19	65	14
14	**1a**	**8c**	20	8	24	<3[a]
15	**1a**	**8a**	20	11	30	12

[a] Analysis of the corresponding allyl alcohol by means of GC; **9b** and **9c** were transformed into the corresponding allyl alcohols by reduction with $LiAlH_4$ (8 equiv) in THF (24 h, rt).

3. Conclusion

The enantiomerically pure 2-*N*-methylamino-2,3-dimethylbutanamides **6** can be prepared by selective methylation of amino group in (*R*)- and (*S*)-2-amino-2,3-dimethylbutanamides in high yields (75–80%). The chemoselective introduction of methyl group relies on two reductive aminations, the first being reductive benzylation and the second reductive methylation. This method makes use of the fact that the reductive benzylation is not accompanied by dibenzylation even in the presence of excess benzaldehyde. Hydrogenolytic removal of the benzyl group gave the required enantiomerically pure compounds **6**, which were transformed into enantiomerically pure (*R*)- and (*S*)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridines **7**. The coordination compounds of **7** with Cu(I) catalyze the allyl oxidation with high chemoselectivity ($\leqslant$99%) but very low enantioselectivity ($\leqslant$22% ee).

4. Experimental

4.1. General

Racemic and enantiomerically pure 2-amino-2,3-dimethylbutanamides **3** were prepared according to the method reported by Wepplo.[8] The other reagents for the syntheses were purchased reagent grade and were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500.13 (^{1}H) and 125.76 MHz (^{13}C) in DMSO-d_6. The ^{1}H and ^{13}C chemical shifts were referenced to the central peaks of the solvent (δ = 2.55 and 39.60, respectively). The mass spectra were recorded on an instrument set from Agilent Technologies (gas chromatograph 6890N with mass detector 5973 Network). The elemental analyses were performed on FISONS Instruments EA 1108 CHN. The optical rotation was measured on a Perkin–Elmer 341 instrument, concentration *c* is given in g/100 ml. The enantiomeric purity of cyclopent-2-enyl benzoate **9a** was determined by means of HPLC using a Chiralcel OD-H column (Daicel) (99.5:0.5 hexane/propan-2-ol, 0.5 ml/min, 220 nm) and the enantiomeric purity of cyclohex-2-en-1-ol and cyclohept-2-en-1-ol was determined by means of GC using a Supelco β-DEX 120 column.

4.2. Synthesis of compounds 4–7

4.2.1. (±)-2-*N*-Benzylamino-2,3-dimethylbutanamide (±)-4

A mixture of (±)-2-amino-2,3-dimethylbutanamide (±)-**3** (3.7 g, 28 mmol), benzaldehyde (3.86 g, 36 mmol, 1.3 equiv) and acetic acid (2.75 ml) in methanol (60 ml) was treated with $NaBH_3CN$ (3.0 g, 48 mmol, 1.3 equiv) added for 5 min. After 48-h stirring at room temperature, the solvent was evaporated in vacuo, and the evaporation residue was mixed with 5% aqueous solution of NaOH (50 ml). The mixture obtained was extracted with CH_2Cl_2 (3 × 70 ml), and the combined extracts were evaporated until dry. The crude product was made rid of benzyl alcohol in vacuum at 110 °C and then recrystallized from a mixture of cyclohexane and $CHCl_3$ (10:1). Yield 5.25 g (85%); mp 122–124 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.89 (d, ^{3}J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 0.95 (d, ^{3}J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 1.10 (s, 3H, *CH*$_3$), 1.88 (sp, ^{3}J = 6.9 Hz, 1H, *i*Pr*CH*), 2.17 (br s, 1H, N*H*), 3.65–3.51 (m, 2H, C*H*$_2$), 7.09 (br s, 1H, CON*H*$_2$), 7.26 (t, ^{3}J = 7.0 Hz, 1H, Ph*H*$_4$), 7.31 (br s, 1H, CON*H*$_2$), 7.35 (t, ^{3}J = 7.5 Hz, 2H, Ph*H*$_{3,5}$), 7.39 (t, ^{3}J = 7.1 Hz, 2H, Ph*H*$_{2,6}$); ^{13}C NMR (DMSO-d_6, δ ppm): 15.8; 17.0; 17.7; 35.4; 47.5; 64.6; 126.5; 127.9; 128.2; 141.6; 178.1; EI-MS: *m*/*z* 176, 132, 106, 91 (100%), 65; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.95; H, 9.29; N, 12.63.

4.2.2. (*R*)-2-*N*-Benzylamino-2,3-dimethylbutanamide (−)-4

Yield 96%; mp 146–149 °C; $[\alpha]_D^{20} = -16.8$ (*c* 0.40, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.87 (d, ^{3}J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 0.95 (d, ^{3}J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 1.10 (s, 3H, *CH*$_3$), 1.88 (sp, ^{3}J = 6.7 Hz, 1H, *i*Pr*CH*), 2.21 (br s, 1H,

N*H*), 3.63–3.51 (2 × d, ^2J = 12.9 Hz, 2H, CH_2), 7.07 (br s, 1H, CONH_2), 7.26 (t, ^3J = 7.1 Hz, 1H, PhH_4), 7.30 (br s, 1H, CONH_2), 7.35 (t, ^3J = 7.3 Hz, 2H, Ph$H_{3,5}$), 7.39 (t, ^3J = 7.1 Hz, 2H, Ph$H_{2,6}$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.8; 17.0; 17.7; 35.4; 47.5; 64.6; 126.5; 127.9; 128.2; 141.6; 178.1; EI-MS: *m*/*z* 176, 132, 106, 91 (100%), 65; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.83; H, 9.38; N, 12.87.

4.2.3. (*S*)-2-*N*-Benzylamino-2,3-dimethylbutanamide (+)-4

Yield 97%; mp 146–148 °C; $[\alpha]_D^{20} =$+16.7 (*c* 0.41, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.87 (d, ^3J = 6.6 Hz, 3H, *i*Pr*CH*$_3$), 0.95 (d, ^3J = 6.6 Hz, 3H, *i*Pr*CH*$_3$), 1.10 (s, 3H, *CH*$_3$), 1.88 (sp, ^3J = 6.6 Hz, 1H, *i*Pr*CH*), 2.20 (br s, 1H, N*H*), 3.64 – 3.51 (2 × d, ^2J = 12.8 Hz, 2H, CH_2), 7.07 (br s, 1H, CONH_2), 7.26 (t, ^3J = 6.9 Hz, 1H, PhH_4), 7.30 (br s, 1H, CONH_2), 7.35 (t, ^3J = 7.2 Hz, 2H, Ph$H_{3,5}$), 7.39 (t, ^3J = 7.2 Hz, 2H, Ph$H_{2,6}$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.8; 17.0; 17.7; 35.4; 47.5; 64.6; 126.5; 127.9; 128.2; 141.6; 178.1; EI-MS: *m*/*z* 176, 132, 106, 91 (100%), 65; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.68; H, 9.33; N, 12.83.

4.2.4. (±)-2-*N*-Benzyl-*N*-methylamino-2,3-dimethylbutanamide (±)-5

A mixture of compound (±)-**4** (5.25 g, 24 mmol), 37% aqueous formaldehyde solution (4.2 g, 52 mmol), acetic acid (2 ml) and methanol (80 ml) was treated with $NaBH_3CN$ (1.95 g, 33 mmol) added over 5 min. The mixture was stirred at room temperature 24 h, whereupon another formaldehyde solution (6.2 g, 52 mmol) was added. After 16 h, methanol was evaporated in vacuum, and the evaporation residue was mixed with 5% aqueous solution of NaOH (50 ml). The mixture formed was extracted with CH_2Cl_2 (4 × 70 ml), and the combined extracts were dried and evaporated until dry. Yield 5.10 g (91%) of an oily product, which solidified after several days; mp 80–81 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.92 (d, ^3J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 1.01 (d, ^3J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 1.16 (s, 3H, *CH*$_3$), 2.05 (s, 3H, N*CH*$_3$), 2.16 (sp, ^3J = 6.7 Hz, 1H, *i*Pr*CH*), 3.60–3.43 (2 × d, ^2J = 14.3 Hz, 2H, CH_2), 6.90 (br s, 1H, CONH_2), 7.20 (br s, 1H, CONH_2), 7.27 (t, ^3J = 7.2 Hz, 1H, PhH_4), 7.36 (t, ^3J = 7.4 Hz, 2H, Ph$H_{3,5}$), 7.43 (d, ^3J = 7.5 Hz, 2H, Ph$H_{2,6}$). ^{13}C NMR (DMSO-d_6, δ ppm): 12.4; 17.8; 17.9; 32.1; 35.4; 55.5; 68.8; 126.7; 127.9; 128.4; 140.2; 174.1; EI-MS: *m*/*z* 190, 174, 160, 120, 91 (100%), 65, 56; Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.92; H, 9.38; N, 12.05.

4.2.5. (*R*)-2-*N*-Benzyl-*N*-methylamino-2,3-dimethylbutanamide (−)-5

Yield 93%; mp 96–99 °C; $[\alpha]_D^{20} = -13.1$(*c* 0.42, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.91 (d, ^3J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 1.01 (d, ^3J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 1.16 (s, 3H, *CH*$_3$), 2.05 (s, 3H, N*CH*$_3$), 2.16 (sp, ^3J = 6.8 Hz, 1H, *i*Pr*CH*), 3.59–3.43 (2 × d, ^2J = 14.2 Hz, 2H, CH_2), 6.91 (br s, 1H, CONH_2), 7.22 (br s, 1H, CONH_2), 7.27 (t, ^3J = 7.2 Hz, 1H, PhH_4), 7.36 (m, 2H, Ph$H_{3,5}$), 7.43 (d, ^3J = 7.5 Hz, 2H, Ph$H_{2,6}$). ^{13}C NMR (DMSO-d_6, δ ppm): 12.4; 17.8; 17.9; 32.1; 35.4; 55.5; 68.8; 126.7; 127.9; 128.4; 140.2; 174.1; EI-MS: *m*/*z* 190, 174, 160, 120, 91 (100%), 65, 56; Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 72.04; H, 9.33; N, 11.84.

4.2.6. (*S*)-2-*N*-Benzyl-*N*-methylamino-2,3-dimethylbutanamide (+)-5

Yield 92%; mp 94–97 °C; $[\alpha]_D^{20} = +12.9$(*c* 0.42, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.92 (d, ^3J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 1.01 (d, ^3J = 6.7 Hz, 3H, *i*Pr*CH*$_3$), 1.16 (s, 3H, *CH*$_3$), 2.05 (s, 3H, N*CH*$_3$), 2.14 (sp, ^3J = 6.7 Hz, 1H, *i*Pr*CH*), 3.59–3.44 (2 × d, ^2J = 14.2 Hz, 2H, CH_2), 6.91 (br s, 1H, CONH_2), 7.23 (br s, 1H, CONH_2), 7.27 (t, ^3J = 6.8 Hz, 1H, PhH_4), 7.36 (m, 2H, Ph$H_{3,5}$), 7.43 (d, ^3J = 7.4 Hz, 2H, Ph$H_{2,6}$). ^{13}C NMR (DMSO-d_6, δ ppm): 12.5; 17.9; 18.0; 32.2; 35.4; 55.5; 68.8; 126.7; 127.9; 128.4; 140.3; 174.1; EI-MS: *m*/*z* 190, 174, 160, 120, 91 (100%), 65, 56; Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.87; H, 9.21; N, 11.75.

4.2.7. (±)-2-*N*-Methylamino-2,3-dimethylbutanamide (±)-6

Catalyst (5% palladium on carbon 0.23 g, 0,1 mmol Pd) was added to a solution of compound (±)-**5** (2.34 g, 10 mmol) in methanol (60 ml), and hydrogen (ca. 5 kPa) was bubbled through the mixture for a period of 48 h, whereupon the mixture was bubbled with argon, filtered and the product was isolated by evaporation of methanol. Yield 1.35 g (94%); mp 58–60 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.82 (d, ^{3}J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 0.88 (d, ^{3}J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 1.00 (s, 3H, *CH*$_3$), 1,76 (sp, ^{3}J = 6.9 Hz, 1H, *i*Pr*CH*), 1.87 (br s, 1H, N*H*), 2.15 (s, 3H, N*CH*$_3$), 6.96 (br s, 1H, CON*H*$_2$), 7.18 (br s, 1H, CON*H*$_2$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.1; 16.8; 17.6; 30.0; 35.4; 64.4; 177.9; EI-MS: *m*/*z* 129, 100 (100%), 85, 69, 56; Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.42. Found: C, 58.47; H, 11.03; N, 19.36.

4.2.8. (*R*)-2-*N*-Methylamino-2,3-dimethylbutanamide (+)-6

Yield 86%; mp 87–89 °C; $[\alpha]_D^{20} = +13.9$ (*c* 0.47, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.82 (d, ^{3}J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 0.88 (d, ^{3}J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 0.99 (s, 3H, *CH*$_3$), 1.76 (sp, ^{3}J = 6.8 Hz, 1H, *i*Pr*CH*), 1.84 (br s, 1H, N*H*), 2.15 (s, 3H, N*CH*$_3$), 6.97 (br s, 1H, CON*H*$_2$), 7.19 (br s, 1H, CON*H*$_2$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.3; 16.9; 17.7; 30.2; 35.5; 64.6; 178.0; EI-MS: *m*/*z* 129, 100 (100%), 85, 69, 56; Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.42. Found: C, 58.53; H, 11.12; N, 19.27.

4.2.9. (*S*)-2-*N*-Methylamino-2,3-dimethylbutanamide (−)-6

Yield 90%; mp 85–86 °C; $[\alpha]_D^{20} = -14.2$ (*c* 0.48, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.82 (d, ^{3}J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 0.88 (d, ^{3}J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 0.99 (s, 3H, *CH*$_3$), 1,75 (sp, ^{3}J = 6.9 Hz, 1H, *i*Pr*CH*), 1.86 (br s, 1H, N*H*), 2.15 (s, 3H, N*CH*$_3$), 6.95 (br s, 1H, CON*H*$_2$), 7.17 (br s, 1H, CON*H*$_2$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.2; 16.8; 17.6; 30.1; 35.4; 64.6; 177.9; EI-MS: *m*/*z* 129, 100 (100%), 85, 69, 56; Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.42. Found: C, 58.41; H, 11.09; N, 19.24.

4.2.10. (±)-(5-Isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridine (±)-7

At 0 °C, a solution of picolinic acid (0.92 g, 7.5 mmol) and DMAP (0.91 g, 7.5 mmol) in dry CH_2Cl_2 (15 ml) was mixed with diisopropylcarbodiimide (1.18 ml, 7.5 mmol). After 30-min stirring, a solution of compound (±)-**6** (1.08 g, 7.5 mmol) in CH_2Cl_2 (15 ml) was added, and the mixture was stirred for another 3–4 h at 0 °C and then 4 days at room temperature. The suspension formed was extracted with 5% aqueous solution of acetic acid (30 ml). After evaporating CH_2Cl_2, the evaporation residue was suspended in 1 M NaOH (50 ml), the suspension was stirred for 1 h, neutralized with acetic acid and then extracted with diethyl ether (3 × 30 ml). The crude product obtained by evaporating the diethyl ether was recrystallized from cyclohexane. Yield 1.01 g (58%); mp 106–108 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.81 (d, ^{3}J = 7.0 Hz, 3H, *i*Pr*CH*$_3$), 1.06 (d, ^{3}J = 7.0 Hz, 3H, *i*Pr*CH*$_3$), 1.39 (s, 3H, *CH*$_3$), 2.13 (sp, ^{3}J = 7.0 Hz, 1H, *i*Pr*CH*), 3.38 (s, 3H, N*CH*$_3$), 7.71 (m, 1H, Py*H*$_4$), 8.13 (m, 2H, Py*H*$_{3,5}$), 8.85 (m, 1H, Py*H*$_6$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.1; 16.5; 19.2; 30.4; 32.5; 71.4; 126.4; 126.7; 137.6; 148.5; 148.9; 173.7; 192.4; EI-MS: *m*/*z* 231 (M+), 216, 188 (100%), 173, 105, 78; Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.27; H, 7.63; N, 18.46.

4.2.11. (*R*)-(5-Isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridine (+)-7

Yield 65%; mp 128–131 °C; $[\alpha]_D^{20} = +68.1$ (*c* 0.50, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.81 (d, ^{3}J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 1.05 (d, ^{3}J = 6.8 Hz, 3H, *i*Pr*CH*$_3$), 1.39 (s, 3H, *CH*$_3$), 2.12 (sp, ^{3}J = 6.8 Hz, 1H, *i*Pr*CH*), 3.41 (s, 3H, N*CH*$_3$), 7.70 (m, 1H, Py*H*$_4$), 8.13 (m, 2H, Py*H*$_{3,5}$), 8.84 (m, 1H, Py*H*$_6$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.2; 16.6; 19.4; 30.6; 32.7; 71.6; 126.6; 126.9; 137.8; 148.5; 149.1; 173.9; 192.6; EI-MS: *m*/*z* 231 (M+), 216, 188 (100%), 173, 105, 78; Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.47; H, 7.49; N, 18.20.

4.2.12. (*S*)-(5-Isopropyl-1,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-on-2-yl)pyridine (−)-7

Yield 62%; mp 127–130 °C; $[\alpha]_D^{20} = -68.0$ (*c* 0.51, THF); ^{1}H NMR (DMSO-d_6, δ ppm): 0.81 (d, ^3J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 1.05 (d, ^3J = 6.9 Hz, 3H, *i*Pr*CH*$_3$), 1.38 (s, 3H, *CH*$_3$), 2.12 (sp, ^3J = 6.9 Hz, 1H, *i*Pr*CH*), 3.39 (s, 3H, N*CH*$_3$), 7.71 (m, 1H, Py*H*$_4$), 8.13 (m, 2H, Py*H*$_{3,5}$), 8.85 (m, 1H, Py*H*$_6$). ^{13}C NMR (DMSO-d_6, δ ppm): 15.1; 16.5; 19.3; 30.5; 32.5; 71.6; 126.6; 126.8; 137.7; 148.6; 149.0; 173.9; 192.6; EI-MS: *m*/*z* 231 (M+), 216, 188 (100%), 173, 105, 78; Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.41; H, 7.57; N, 17.94.

4.3. X-ray

Crystallographic data (excluding structure factors) for structures (*R*)-(+)-**6** and (*R*)-(+)-**7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 670558 (*R*)-(+)-**6** and CCDC 670559 (*R*)-(+)-**7**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htlm or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223336033 or deposit@ccdc.cam.ac.uk. The X-ray data were collected on a Nonius KappaCCD diffractometer fitted with MoK_α radiation (λ = 0.71073 Å) at 150(1) K. The absorption correction was performed using a empirical (SADABS for (*R*)-(+)-**6**)[15a] and [15b] and gaussian procedure [(*R*)-(+)-**7**],[15c] respectively, the structure was solved by direct methods (SIR92[16]) and full-matrix least-squares refinements on F^2 were carried out using the program SHELXL 97.[17] Flack parameter[18] was optimized to zero value with known chemical absolute configuration *R* for both structures.

Crystallographic data for (*R*)-(+)-**6**. $C_7H_{16}N_2O$, M = 144.22, T = 150(1) K. Monoclinic, space group $P2_1$ with a = 6.0690(16), b = 9.5230(16), c = 7.693(2) Å, β = 102.13(2)°, V = 434.70(18) Å^{-3}, Z = 2, D_x = 1.102 g cm^{-3} (Z = 2), F(0 0 0) = 160, μ = 0.075 mm^{-1} (corrected by SADABS (T_{min}/T_{max} 0.379483)), 7359 reflections measured (θ_{max} = 27.5°), 1038 independent (R_{int} = 0.074), 901 with $I > 2\sigma(I)$, 92 parameters, S = 1.013, R_1 (obs. data) = 0.0757, wR_2 (*all data*) = 0.1944; max, min residual electron density = 0.579, −0.409 eÅ^{-3}.

Crystallographic data for (*R*)-(+)-**7**. $C_{13}H_{18}N_3O$, M = 232.30, T = 150(1) K. Orthorhombic, space group $P2_12_12_1$ with a = 9.6820(9), b = 11.1320(9), c = 11.6440(4) Å, V = 1254.99(16) Å^{-3}, Z = 4, D_x = 1.224 g cm^{-3} (Z = 4), F(0 0 0) = 496, μ = 0.080 mm^{-1}, T_{min} = 0.979, T_{max} = 0.990; 3325 reflections measured (θ_{max} = 27.5°), 1641 independent (R_{int} = 0.0394), 1280 with $I > 2\sigma(I)$, 92 parameters, S = 1.187, R_1 (obs. data) = 0.0595, wR_2 (*all data*) = 0.1307; max, min residual electron density = 0.230, −0.230 e Å^{-3}.

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