Organocatalysis of asymmetric aldol reaction in water: comparison of catalytic properties of (*S*)-valine and (*S*)-proline amides*

*A. S. Kucherenko,[a] D. E. Siyutkin,[a] R. R. Dashkin,[b] and S. G. Zlotin[a]**

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5328. E-mail: zlotin@ioc.ac.ru*
[b]*D. I. Mendeleev University of Chemical Technology of Russia, 9 Miusskaya pl., 125047 Moscow, Russian Federation. Fax: +7 (495) 490 7523. E-mail: zlotin@ioc.ac.ru*

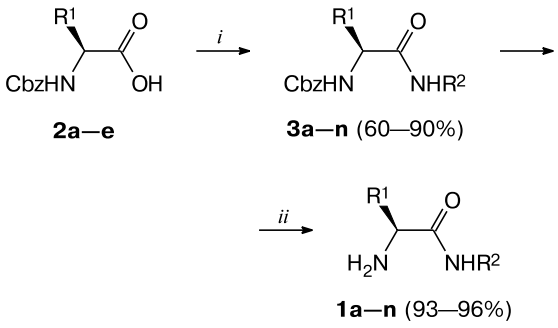
(*S*)-Valine amides containing (*S*)- or (*R*)-α-phenylethyl substituents at N^1 atom efficiently catalyze asymmetric aldol reactions between cyclic (heterocyclic) ketones and aromatic aldehydes in water, predominantly giving rise to the aldol *anti*-diastereomers in high yields (up to 98%) and enantiomeric excess (up to 94%).

Key words: organocatalysis, asymmetric aldol reaction, (α)-amino amides, water.

An asymmetric aldol reaction is one of the most simple and convenient methods for the enantioselective formation of carbon—carbon bonds in organic compounds.[1—3] The class I aldolases, *i.e.*, the peptides whose active centers contain amino acids with primary amino groups (serine and lysine), are natural catalysts for this reaction (synthesis of carbohydrates).[4—7] Amino acid proline[8] and its derivatives, including amides,[9] as well as proline-containing lower peptides,[10] are commonly used as the laboratory catalysts (organocatalysts). In this case, unlike the enzyme reactions taking place in aqueous solutions,[11] the reactions in the presence of proline derivatives, as a rule, are carried out in organic solvents.[8a,e] In the last decade, proline amides were obtained,[12] which, like aldolases, enantioselectively catalyzed asymmetric aldol reactions between aldehydes and ketones in the presence of water. However, despite of the natural analogies, only a few examples of organocatalysis by α-amino amides bearing primary amino groups in aqueous solutions are reported.[13] As far as we know, catalytic properties of primary and secondary α-amino amides have not been compared under these conditions.

To partly fill this gap, we synthesized (Scheme 1) natural (*S*)-α-amino amides **1a**—**n** containing various amino acid fragments (Phe, Val, Leu, Ile, Trp) and simple aromatic, fatty aromatic, or alicyclic substituents at the nitrogen atom of the amide group. These compounds were not studied earlier as organocatalysts of asymmetric aldol reactions in water. A two-step synthesis included amida-

Scheme 1



2: Bn (**a**), $CHMe_2$ (**b**), CH_2CHMe_2 (**c**), CH(Me)Et (**d**), 3-indolylmethyl (**e**)

Compound **1**, **3**	R^1	R^2
a	Bn	Ph
b	$CHMe_2$	Ph
c	CH_2CHMe_2	Ph
d	CH(Me)Et	Ph
e	3-indolylmethyl	Ph
f	$CHMe_2$	4-$MeOC_6H_4$
g	$CHMe_2$	4-$AcNHC_6H_4$
h	$CHMe_2$	2-$AcNHC_6H_4$
i	$CHMe_2$	2-FC_6H_4
j	$CHMe_2$	Bn
k	$CHMe_3$	$CHPh_2$
l	$CHMe_2$	Terp*
m	$CHMe_2$	(*S*)-CH(Ph)Me
n	$CHMe_2$	(*R*)-CH(Ph)Me

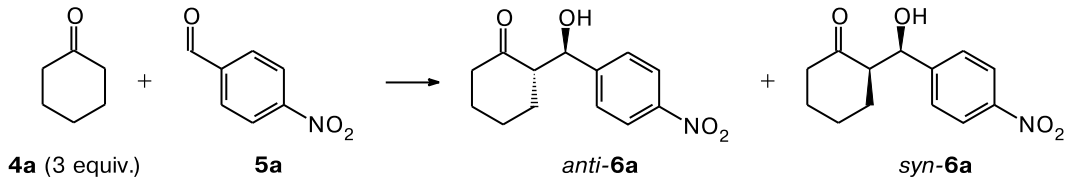
* Terp stands for (1*S*,2*S*,3*R*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl

Reagents and conditions: *i*. R^2NH_2, ClCOOEt, NEt_3, THF, 20 °C, 12 h; *ii*. H_2 (1 atm.), 5% Pd/C, MeOH, 20 °C, 3 h.

* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya on the occasion of her anniversary.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 1010—1014, April, 2013.

Scheme 2



Reagents and conditions: **1** or **7** (20 mol.%), H_2O (100 equiv.), 20 °C, 20 h.

tion of commercially available *N*-Cbz-protected α-amino acids **2** followed by the catalytic (H_2, Pd/C) hydrogenolysis (deprotection) of compounds **3a**—**n**.

The catalytic activity of compounds **1** was studied in the reaction between cyclohexanone (**4a**) and 4-nitrobenzaldehyde (**5a**) in aqueous solutions (Scheme 2). The reactions were carried out at room temperature at the molar ratio **4a** : **5a** : H_2O = 3 : 1 : 100, using 20 mol.% of the catalyst (Table 1). First, we compared the catalytic properties of anilides of (*S*)-Phe (**1a**), (*S*)-Val (**1b**), (*S*)-Leu (**1c**), (*S*)-Ile (**1d**), and (*S*)-Trp (**1e**) (entries *1*—*5*). In all the cases, the mixtures of *anti*- and *syn*-diastereomeric aldols **6a** were formed in high yields (^{1}H NMR data). The enantiomeric excess of *anti*-aldol, as a rule, was higher than that of the corresponding *syn*-isomer and reached the maximum value (93%) in the case when (*S*)-valine anilide (**1b**) was used as organocatalyst.

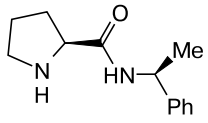
Table 1. Asymmetric aldol reaction between compounds **4a** and **5a** in aqueous solutions catalyzed by primary α-amino amides **1a**—**n** or proline amides **7a**,**b**

Entry	Catalyst	Yield of **6a**[a] (%)	*anti : syn*[b] (%)[c]	*ee anti/syn*
1	**1a**	90	30 : 70	32/46
2	**1b**	93	52 : 48	93/0
3	**1c**	95	50 : 50	30/16
4	**1d**	95	50 : 50	30/4
5	**1e**	75	58 : 42	80/44
6	**1f**	74	64 : 36	89/16
7	**1g**	12[d]	80 : 20	93/2
8	**1h**	14[d]	83 : 17	87/6
9	**1i**	17[d]	90 : 10	97/—
10	**1j**	84	60 : 40	92/2
11	**1k**	98	55 : 45	88/48
12	**1l**	98	60 : 40	40/19
13	**1m**	81	71 : 29	92/10
14	**1n**	80	78 : 22	93/20
15	**7a**	96	74 : 26	54/2
16	**7b**	94	60 : 40	80/21
17[e]	**1n**	90	80 : 20	94/6
18[f]	**1n**	60	85 : 15	95/64
19[g]	**1n**	>95	40 : 60	13/12

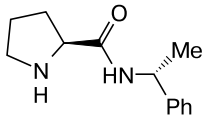
[a] The yield of a mixture of *anti*- and *syn*-diastereomers of compounds **6a** after column chromatography on silica gel.
[b] According to the ^{1}H NMR spectra of the reaction mixture.
[c] According to the HPLC data.
[d] The conversion according to the ^{1}H NMR spectroscopic data.
[e] The reaction was carried out at 0 °C, the reaction time 30 h.
[f] The reaction was carried out in the presence of CF_3CO_2H (20 mol.%).
[g] The reaction was carried out without solvent.

In this reaction, the catalytic efficiency of valine derivatives **1f**—**n** depended on the substituent at the nitrogen atom (see Table 1, entries *6*—*14*). The most selective of them (*anti : syn* = 90 : 10, *ee* 97%) was *N*-(2-fluorophenyl) amide **1i**. However, this catalyst, as well as compounds **1g** and **1h** containing acetamide groups at *para*- or *ortho*-positions of the aromatic ring, exhibited low activity under selected conditions (the conversion was 12—17%). In the presence of valine amide **1l** containing a hydroxypinane fragment, the reaction showed low enantioselectivity (entry *12*). Valine (*S*)- and (*R*)-α-phenylethylamides **1m** and **1n** exhibited better catalytic performance, which is only slightly inferior to compound **1i** in the diastereo- and enantioselectivity, giving 80—81% yield of aldol **6a** (entries *13*, *14*).

Then, we compared in the model reaction (*S*)-valine amides **1m** and **1n** with the corresponding (*S*)-proline amides **7a** and **7b** containing (*S*)- and (*R*)-α-phenylethyl substituents (see Scheme 2, Table 1, entries *15*, *16*). The proline-containing catalysts **7a** and **7b** exceeded valine amides **1m** and **1n** in their activity in aqueous solutions, however, the enantiomeric excess of the major *anti*-diastereomer of aldol **6a** in the case of **7a**,**b** was lower. We succeeded in the increase of the *anti*-diastereo- and enantioselectivity of the reaction catalyzed by valine amide **1n** by carrying it out at 0 °C (entry *17*), as well as by the addition of CF_3CO_2H as a co-catalyst (entry *18*). Water plays an important role in the systems under study: when the model reaction was carried out under neat conditions, its enantioselectivity was considerably lower, with the *syn*-diastereomer of aldol **6a** being the major product (entry *19*).



7a

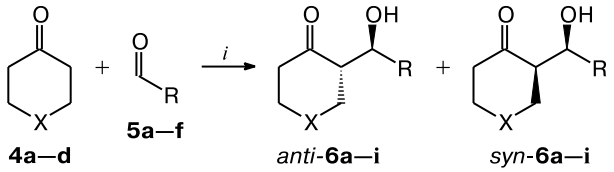


7b

Valine amide **1n** appeared suitable catalyst of the asymmetric aldol reactions between cyclic ketones **4a—d** and aromatic (heteroaromatic) aldehydes **5a—f** in water (Scheme 3, Table 2). The yields of products **6a—i** and the selectivity of the reactions depended on the structure of carbonyl compounds. Cyclohexanone **4a** reacted with benzaldehyde derivative **5a—e** containing electron-withdrawing or electron-donating substituents in the aromatic ring to afford the corresponding *anti*-aldols **6a—e** with moderate diastereoselectivity and high enantioselectivity (see Table 2, entries *1—5*). The enantioselectivity of **1n**-catalyzed reactions involving 2-pyridinecarboxaldehyde (**5f**), cyclopentane (**4b**), and heterocyclic ketones **4c**,**d** was somewhat lower.

In conclusion, we found that (*S*)-valine amide **1n** containing the (*R*)-α-phenylethyl group at the amide nitrogen atom is comparable with the corresponding (*S*)-proline amide in the efficiency and selectivity of the catalytic action in the asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in aqueous media. The results obtained indicate that a search for the new efficient organocatalysts bearing primary α-amino amide moieties is a promising direction.

Scheme 3



Compound **4**	X
a	CH_2
b	σ-bond
c	O
d	S

Compound **5**	R
a	4-$O_2NC_6H_4$
b	2-$O_2NC_6H_4$
c	4-$MeOC(O)C_6H_4$
d	4-$MeOC_6H_4$
e	C_6F_5
f	2-pyridyl

Compound **6**	X	R
a	CH_2	4-$O_2NC_6H_4$
b	CH_2	2-$O_2NC_6H_4$
c	CH_2	4-$MeOC(O)C_6H_4$
d	CH_2	4-$MeOC_6H_4$
e	CH_2	C_6F_5
f	CH_2	2-pyridyl
g	σ-bond	4-$O_2NC_6H_4$
h	O	4-$O_2NC_6H_4$
i	S	4-$O_2NC_6H_4$

Reagents and conditions: 1n (20 mol.%), H_2O (100 equiv.), 0 °C, 30—120 h.

Table 2. The use of catalyst **1n** in asymmetric aldol reactions in water

Entry	Reactants	*t*/h	Product	Yield[a] (%)	*anti* : syn[b] (%)	*ee anti* : *syn*[c] (%)
1	**4a**+**5a**	30	**6a**	90	80 : 20	94/6
2	**4a**+**5b**	60	**6b**	86	70 : 30	94/53
3	**4a**+**5c**	60	**6c**	93	60 : 40	94/61
4	**4a**+**5d**	120	**6d**	17	67 : 33	89/—
5	**4a**+**5e**	60	**6e**	95	83 : 17	88/—
6	**4a**+**5f**	60	**6f**	98	45 : 55	61/24
7	**4b**+**5a**	80	**6g**	96	67 : 33	48/16
8	**4c**+**5a**	80	**6h**	63	60 : 40	63/14
9	**4d**+**5a**	80	**6i**	75	62 : 38	72/36

[a] The yield of a mixture of *anti*- and *syn*-diastereomers of compounds **6** after column chromatography on silica gel.
[b] According to the ^1H NMR spectra of the reaction mixture.
[c] According to the HPLC data.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer (300.13 and 125.76 MHz) in $CDCl_3$ and DMSO-d_6. Chemical shifts of ^1H and ^{13}C nuclei are measured relative to Me_4Si and $CDCl_3$, respectively. Specific angles of rotation $[\alpha]_D^{20}$ were measured on a Jasco DIP-360 polarimeter at 589 nm. Silica gel 0.060—0.200 nm (Acros Organics) was used for column chromatography. Solvents were purified by standard methods.

N^2-Cbz-protected amides of α-amino acids 3 (general procedure). Ethyl chloroformate (0.88 g, 8.0 mmol) was added dropwise to a solution of *N*-(benzyloxycarbonyl)amino acid **2** (8.0 mmol) and NEt_3 (0.81 g, 8.0 mmol) in THF (30 mL) with stirring over 15 min at 0 °C. After 30 min, the corresponding amine (8.0 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C, kept for 16 h at room temperature, and diluted with ethyl acetate (30 mL). A precipitate was filtered off, the filtrate was concentrated, the residue was washed with Et_2O (2×8 mL), dried for 5 h *in vacuo* (10 Torr) at 60 °C. Compounds **3** were obtained as colorless powders. New compounds **3g—i**,**k—n** were characterized by ^1H and ^{13}C NMR and microanalysis data. The structure and purity of known compounds **3a—f**,**j** were confirmed by the comparison of their ^1H NMR spectra and melting points (in the case of compounds **3a—c**,**e**,**j**) with the reported data.

Benzyl (*S*)-*N*-(2-phenyl-1-phenylcarbamoylethyl)carbamate (3a). The yield was 85%, m.p. 168 °C (*cf.* Ref. 14: 169—170 °C).

Benzyl (*S*)-*N*-(2-methyl-1-phenylcarbamoylpropyl)carbamate (3b). The yield was 80%, m.p. 182—184 °C (*cf.* Ref. 15: 182—183 °C).

Benzyl (*S*)-*N*-(3-methyl-1-phenylcarbamoylbutyl)carbamate (3c). The yield was 83%, m.p. 140 °C (*cf.* Ref. 15: 138—141 °C).

Benzyl (*S*)-*N*-(2-methyl-1-phenylcarbamoylbutyl)carbamate (3d).[16] The yield was 90%, m.p. 199—200 °C.

Benzyl (*S*)-*N*-[2-(1*H*-indol-3-yl)-1-phenylcarbamoylethyl]carbamate (3e). The yield was 70%, m.p. 171 °C (*cf.* Ref. 17: 172—173 °C).

Benzyl (*S*)-*N*-[1-(4-methoxyphenylcarbamoyl)-2-methylpropyl]carbamate (3f)[18]. The yield was 86%, m.p. 176 °C.

Benzyl (*S*)-*N*-[1-(4-acetylaminophenylcarbamoyl)-2-methylpropyl]carbamate (3g). The yield was 60%, m.p. >230 °C; $[\alpha]^{20}_D$ +84.40° (*c* 0.1, MeOH). Found (%): C, 65.61; H, 6.42; N, 10.89. $C_{21}H_{25}N_3O_4$. Calculated (%): C, 65.78; H, 6.57; N, 10.96. ^1H NMR (DMSO-d_6), δ: 0.90 (dd, 6 H, J = 6.6 Hz); 2.0 (s, 3 H); 4.0 (t, 1 H, J = 8.0 Hz); 5.0 (s, 2 H); 7.13—7.60

(m, 11 H, Ar and NH); 9.8 (s, 1 H); 9.9 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 18.48, 19.19, 23.88, 30.36, 61.02, 61.45, 119.38, 119.37, 119.67, 127.69, 127.76, 128.32, 134.05, 134.95, 137.04, 156.25, 167.96, 170.12.

Benzyl (*S*)-*N*-[1-(2-acetylaminophenylcarbamoyl)-2-methylpropyl]carbamate (3h). The yield was 62%, m.p. 223 °C; $[\alpha]^{20}_D$ +66.70° (*c* 0.1, MeOH). Found (%): C, 65.61; H, 6.42; N, 10.89. $C_{21}H_{25}N_3O_4$. Calculated (%): C, 65.78; H, 6.57; N, 10.96. ^{1}H NMR (DMSO-d_6), δ: 0.92 (m, 6 H); 2.09 (m, 1 H); 3.30 (s, 3 H); 3.91 (m, 1 H); 5.05 (m, 2 H); 7.10—7.72 (m, 10 H, Ar and NH); 9.32 (s, 1 H); 9.45 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 18.31, 19.14, 29.66, 61.30, 124.15—128.32, 129.87, 131.38, 136.90, 156.62, 168.77, 170.57.

Benzyl (*S*)-*N*-[1-(2-fluorophenylcarbamoyl)-2-methylpropyl]carbamate (3i). The yield was 70%, m.p. 285—286 °C; $[\alpha]^{20}_D$ −31.30° (*c* 0.1, MeOH). Found (%): C, 66.39; H, 6.23; N, 8.17. $C_{19}H_{21}FN_2O_3$. Calculated (%): C, 66.26; H, 6.15; N, 8.13. ^{1}H NMR (DMSO-d_6), δ: 0.93 (m, 6 H); 2.04 (m, 1 H); 4.16 (t, 1 H, J = 7.7 Hz); 5.05 (s, 1 H); 7.10—7.48 (m, 9 H, Ar); 7.79 (m, 1 H); 9.77 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 18.03, 19.13, 30.44, 60.58, 65.55, 115.50 (d, $^2J_{C-F}$ = 20 Hz); 124.30—128.36, 137.08, 154.0 (d, J_{C-F} = 245 Hz); 156.36, 170.93.

Benzyl (*S*)-*N*-(1-benzylcarbamoyl-2-methylpropyl)carbamate (3j). The yield was 89%, m.p. 168—169 °C (*cf.* Ref. 19: 172—173 °C).

Benzyl (*S*)-*N*-[1-(benzhydrylcarbamoyl)-2-methylpropyl]carbamate (3k). The yield was 85%, m.p. 188—189 °C; $[\alpha]^{20}_D$ +30.45° (*c* 1.0, MeOH). Found (%): C, 74.88; H, 6.62; N, 6.64. $C_{26}H_{28}N_2O_3$. Calculated (%): C, 74.97; H, 6.78; N, 6.73. ^{1}H NMR (DMSO-d_6), δ: 0.85 (m, 6 H); 1.99 (m, 1 H); 4.05 (m, 1 H); 5.08 (s, 2 H); 6.15 (d, 1 H, J = 8.44 Hz); 7.14—7.37 (16 H, Ar); 8.85 (d, 1 H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.07, 19.32, 30.72, 56.15, 60.43, 65.60, 127.03—128.53 (Ar), 137.15, 142.32, 156.29, 170.82.

Benzyl (*S*)-*N*-[((1*S*,2*S*,3*R*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylamino)-3-methyl-1-oxobut-2-yl]carbamate (3l). The yield was 73%, m.p. 121—123 °C; $[\alpha]^{20}_D$ −8.12° (*c* 1.0, $CHCl_3$). Found (%): C, 68.75; H, 8.55; N, 6.93. $C_{23}H_{34}N_2O_4$. Calculated (%): C, 68.63; H, 8.51; N, 6.96. ^{1}H NMR ($CDCl_3$), δ: 0.85 (d, 3 H, J = 7.3 Hz); 1.03 (d, 3 H, J = 7.3 Hz); 1.20 (s, 3 H); 1.24 (s, 6 H); 1.37—1.61 (m, 2 H); 1.90—2.07 (m, 2 H); 2.18—2.32 (m, 2 H); 2.42—2.53 (m, 1 H); 3.81—3.90 (m, 1 H); 4.30—4.41 (m, 1 H); 5.10 (s, 2 H); 5.41 (br.d, 1 H, J = 6.6 Hz); 6.62 (br.d, 1 H, J = 6.2 Hz); 7.24—7.48 (m, 5 H). ^{13}C NMR ($CDCl_3$), δ: 17.96, 18.88, 21.34, 22.44, 26.86, 28.16, 31.80, 34.03, 38.91, 39.71, 49.80, 53.40, 61.36, 69.92, 81.14, 127.95, 128.04, 128.12, 136.47, 158.38, 176.47.

Benzyl *N*-[(1*S*)-2-methyl-1-((1*S*)-1-phenylethylcarbamoyl)propyl]carbamate (3m). The yield was 90%, m.p. 172—173 °C; $[\alpha]^{20}_D$ −49.5° (*c* 1.0, $CHCl_3$). Found (%): C, 71.23; H, 7.26; N, 7.81. $C_{21}H_{26}N_2O_3$. Calculated (%): C, 71.16; H, 7.39; N, 7.90. ^{1}H NMR (DMSO-d_6), δ: 0.79 (d, 6 H, J = 6.6 Hz); 1.33 (d, 3 H, J = 7.0 Hz); 1.90 (m, 1 H); 3.89 (m, 1 H); 4.91 (m, 1 H); 5.05 (s, 1 H); 7.11—7.40 (m, 11 H, Ar); 8.37 (d, 1 H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.09, 19.22, 22.53, 30.57, 47.95, 60.16, 65.41, 125.98—128.35 (10 C, Ar); 137.10, 144.63, 156.2, 170.31.

Benzyl *N*-[(1*S*)-2-methyl-1-((1*R*)-1-phenylethylcarbamoyl)propyl]carbamate (3n). The yield was 88%, m.p. 165 °C; $[\alpha]^{20}_D$ +37.8° (*c* 1.0, $CHCl_3$). Found (%): C, 71.20; H, 7.28; N, 7.79. $C_{21}H_{26}N_2O_3$. Calculated (%): C, 71.16; H, 7.39; N, 7.90. ^{1}H NMR (DMSO-d_6), δ: 0.85 (d, 6 H, J = 6.6 Hz); 1.34 (br.s, 3 H); 1.95 (m, 1 H); 3.89 (m, 1 H); 4.92 (m, 1 H); 5.05 (s, 1 H); 7.11—7.40 (m, 11 H, Ar); 8.31 (d, 1 H, J = 7.30 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.44, 19.22, 22.43, 30.41, 47.85, 60.41, 65.40, 126.02—128.34 (10 C, Ar), 137.00, 144.30, 156.12, 170.38.

Amides 1 (general procedure). A mixture of compound **3** (1.0 g), 5% Pd/C (0.1 g), and MeOH (30 mL) was stirred for 2—3 h under hydrogen atmosphere (1 bar). The catalyst was filtered off, the filtrate was concentrated, the residue was purified on a column with silica gel (eluent hexane — ethyl acetate (1 : 1)). Compounds **1** were obtained as colorless powders or dense oils. New compounds **1g—i,l,m,n** were characterized by ^{1}H and ^{13}C NMR spectra and microanalytical data. The structure and purity of known compounds **1a—f** and **1j—k** were confirmed by the comparison of their ^{1}H NMR spectra and melting points (in the case of compounds **1a**,**e**) with the literature data.

(*S*)-2-Amino-3,*N*-diphenylpropanamide (1a). The yield was 96%, m.p. 71—73 °C (*cf.* Ref. 20: 72—74 °C).

(*S*)-2-Amino-3-methyl-*N*-phenylbutanamide (1b). Colorless oil, yield 97%.[21]

(*S*)-2-Amino-4-methyl-*N*-phenylpentanamide (1c). Colorless oil, yield 98%.[22]

(*S*)-2-Amino-3-methyl-*N*-phenylpentanamide (1d). Colorless oil, yield 96%.[23]

(*S*)-2-Amino-3-(1*H*-indol-3-yl)-*N*-phenylpropanamide (3e). The yield was 88%, m.p. 107—110 °C (*cf.* Ref. 24: 114—116 °C).

(*S*)-2-Amino-*N*-(4-methoxyphenyl)-3-methylbutanamide (1f). Colorless oil, yield 94%.[24]

(*S*)-*N*-(4-Acetylaminophenyl)-2-amino-3-methylbutanamide (1g). The yield was 93%, m.p. 173 °C; $[\alpha]^{20}_D$ +18.90° (*c* 0.1, $CHCl_3$). Found (%): C, 62.54; H, 7.79; N, 16.90. $C_{13}H_{19}N_3O_2$. Calculated (%): C, 62.63; H, 7.68; N, 16.85. ^{1}H NMR ($CDCl_3$), δ: 0.85 (d, 3 H, J = 7.3 Hz); 1.05 (d, 3 H); 1.25 (s, 2 H); 2.10 (s, 3 H); 2.42 (m, 1 H); 3.33 (d, 1 H); 7.40—7.60 (m, 5 H); 9.5 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 17.2, 19.6, 23.8, 31.8, 60.7, 119.4—119.6 (4 C, Ar); 134.1, 134.8, 167.9, 173.6.

(*S*)-*N*-(2-Acetylaminophenyl)-2-amino-3-methylbutanamide (1h). The yield was 95%, m.p. 142 °C; $[\alpha]^{20}_D$ +41.80° (*c* 0.1, $CHCl_3$). Found (%): C, 62.52; H, 7.82; N, 16.88. $C_{13}H_{19}N_3O_2$. Calculated (%): C, 62.63; H, 7.68; N, 16.85. ^{1}H NMR (DMSO-d_6), δ: 0.81 (d, 3 H, J = 7.3 Hz); 0.92 (d, 3 H, J = 7.3 Hz); 2.05 (s, 3 H); 3.15 (m, 1 H); 7.05—7.32 (m, 3 H); 7.79 (d, 1 H, J = 3.4 Hz); 9.51 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 16.1, 19.4, 23.5, 31.1, 60.3, 124.1, 125.4—125.8 (3 C, Ar); 130.0, 130.3, 169.3, 173.9.

(*S*)-2-Amino-*N*-(2-fluorophenyl)-3-methylbutanamide (1i). The yield was 95%, m.p. 158 °C; $[\alpha]^{20}_D$ +38.40° (*c* 0.1, $CHCl_3$). Found (%): C, 62.96; H, 7.27; N, 13.41. $C_{11}H_{15}FN_2O$. Calculated (%): C, 62.84; H, 7.19; N, 13.32. ^{1}H NMR ($CDCl_3$), δ: 0.98 (d, 6 H, J = 7.5 Hz); 2.04 (m, 1 H); 3.45 (m, 1 H, J = 2.7 Hz); 6.97—7.4 (m, 3 H); 8.3—8.4 (t, 1 H, J = 10.0 Hz); 9.75 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 15.8, 19.0, 30.5, 60.4, 114.3, 115.0, 123.7, 124.3, 129.8, 150.9—154.1 (d, CF, J = 245); 172.88.

(*S*)-2-Amino-*N*-benzyl-3-methylbutanamide (1j). Colorless oil, yield 96%.[25]

(*S*)-2-Amino-*N*-benzhydryl-3-methylbutanamide (1k). Colorless oil, yield 95%.[26]

(*S*)-2-Amino-*N*-[(1*S*,2*S*,3*R*,5*R*)-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-3-methylbutanamide (1l). The yield was 73%, m.p. 92 °C; $[\alpha]^{20}_D$ −4.02° (*c* 1.0, $CHCl_3$). Found (%): C, 67.34; H, 10.56; N, 10.38. $C_{15}H_{28}N_2O_2$. Calculated (%):

C, 67.13; H, 10.52; N, 10.44. ^{1}H NMR ($CDCl_3$), δ: 0.88 (d, 3 H, J = 7.3 Hz); 1.02 (d, 3 H, J = 7.3 Hz); 1.09 (s, 3 H); 1.30 (s, 6 H); 1.39—1.55 (m, 2 H); 1.60—1.83 (s, 2 H); 1.91—2.04 (m, 2 H); 2.19—2.33 (m, 2 H); 2.47—2.59 (m, 1 H); 3.22 (d, 1 H, J = 5.1 Hz); 4.36 (q, 1 H, J = 7.1 Hz); 7.62 (d, 1 H, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 16.73, 19.61, 23.69, 28.24, 28.81, 29.88, 31.47, 36.26, 38.81, 40.67, 47.95, 54.77, 60.81, 74.21, 173.85.

(*S*)-2-Amino-3-methyl-*N*-[1-(*S*)-phenylethyl]butanamide (1m). The yield was 96%, m.p. 52—53 °C; $[\alpha]^{20}_D$ +52.20° (*c* 1.0, $CHCl_3$). Found (%): C, 70.75; H, 9.24; N, 12.66. $C_{13}H_{20}N_2O$. C, 70.87; H, 9.15; N, 12.72. ^{1}H NMR ($CDCl_3$), δ: 0.85 (d, 3 H, J = 7.3 Hz); 0.98 (d, 3 H, J = 7.3 Hz); 1.50 (d, 3 H, J = 7.0 Hz); 1.57 (s, 2 H); 2.30 (m, 1 H); 3.22 (d, 1 H, J = 3.7 Hz); 5.13 (m, 1 H); 7.17—7.40 (m, 5 H); 7.64 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 16.0, 19.5, 21.9, 30.8, 48.1, 59.9, 126.0 (2 C), 127.0, 128.4 (2 C), 143.4, 173.2.

(*S*)-2-Amino-3-methyl-*N*-[1-(*R*)-phenylethyl]butanamide (1n). The yield was 94%, m.p. 56—57 °C; $[\alpha]^{20}_D$ −88.2° (*c* 1.0, $CHCl_3$). Found (%): C, 70.78; H, 9.22; N, 12.62. $C_{13}H_{20}N_2O$. Calculated (%): C, 70.87; H, 9.15; N, 12.72. ^{1}H NMR ($CDCl_3$), δ: 0.75 (d, 3 H, J = 7.0 Hz); 0.95 (d, 3 H, J = 7.0 Hz); 1.48 (d, 3 H, J = 6.6 Hz); 1.72 (s, 2 H); 2.25 (m, 1 H); 3.25 (d, 1 H, J = 3.7 Hz); 5.14 (m, 1 H); 7.15—7.42 (m, 5 H); 7.60 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 16.0, 19.5, 21.9, 30.8, 40.1, 59.9, 125.9 (2 C), 126.9, 128.4 (2 C), 143.5, 173.3.

Aldol reactions (general procedure). A mixture of catalyst **1** (0.05 mmol), ketone **4** (0.80 mmol), aldehyde **5** (0.26 mmol), and water (0.5 mL) was stirred at room temperature for the time specified in Tables 1 and 2 (TLC monitoring). The reaction mixture was extracted with Et_2O (2×5 mL), the extracts were filtered through the silica gel pad (1.0 g), the solvent was evaporated (15 Torr). The ratio of *syn*- and *anti*- aldols **6** was determined from the ^{1}H NMR spectra of crude reaction mixture. The mixtures of *syn*- and *anti*-isomers of aldols **6** were purified on a column with silica gel (eluent hexane—ethyl acetate (3 : 1)). ^{1}H NMR spectra of known compounds **6a**—**i** corresponded to the literature data.[27—29] The *ee* values of *anti*- and *syn*-isomers **6** were determined by HPLC on Chiralcel OD-H, OJ-H, or AD chiral phases.

This work was financially supported in parts by the Council on Grants at the President of the Russian Federation (Program of State Support for Young Scientists-Candidates of Science, Grant MK-3551.2012.3), the Russian Academy of Sciences (Program of Basic Research of the Presidium of RAS P-08), and the Russian Foundation for Basic Research (Project Nos 12-03-00420 and 12-03-31805).

References

1. C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.*, 2004, **33**, 65.
2. *Modern Aldol Reactions*, Ed. R. Mahrwald, Vols **1** and **2**, Wiley-VCH, Weinheim, 2004.
3. R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B.-W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, R. B. Chenevert, A. Fliri, K. Frobel, H.-J. Gais, D. G. Garratt, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim, Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Ong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. Williams, H. N.-C. Wong, *J. Am. Chem. Soc.*, 1981, **103**, 3210.
4. H. J. M. Gijsen, L. Qiao, W. Fitz, C. H. Wong, *Chem. Rev.*, 1996, **96**, 443.
5. C. H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem., Int. Ed.*, 1995, **34**, 412.
6. S. M. Dean, W. A. Greenberg, C. H. Wong, *Adv. Synth. Catal.*, 2007, **349**, 1308.
7. D. Martynowski, Y. Eyobo, T. F. Li, K. Yang, A. M. Liu, H. Zhang, *Biochemistry*, 2006, **45**, 10412.
8. (a) B. List, P. Pojarliev, C. Castello, *Org. Lett.*, 2001, **3**, 573; (b) A. Cordova, W. Notz, C. F. Barbas III, *J. Org. Chem.*, 2002, **67**, 301; (c) B. List, *Tetrahedron*, 2002, **58**, 5573; (d) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798; (e) A. Cordova, *Tetrahedron Lett.,* 2004, **45**, 3949; (f) S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.*, 2009, **78**, 737.
9. (a) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, Y. D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262; (b) S. Samanta, J. Liu, R. Dodda, C. Zhao, *Org. Lett.*, 2005, **7**, 5321; (c) Z. Tang, Z. Yang, X. Chen, L. Cun, A. Mi, Y. Jiang, Z. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285; (d) S. Tanimori, T. Naka, M. Kirihata, *Synth. Commun.*, 2004, **34**, 4043; (e) A. Bogevig, N. Kumaragurubaran, K. A. Jorgensen, *Chem. Commun.*, 2002, 620; (f) Y. Q. Fu, Z. C. Li, L. N. Ding, J. C. Tao, S. H. Zhang, M. S. Tang, *Tetrahedron: Asymmetry*, 2006, **17**, 3351; (g) L. He, J. Jiang, Z. Tang, X. Cui, A. Q. Mi, Y. Z. Jiang, L.-Z. Gong, *Tetrahedron: Asymmetry*, 2007, **18**, 265.
10. P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.*, 2005, **7**, 1101.
11. H. J. M. Gijsen, L. Qiao, W. Fitz, C. H. Wong, *Chem. Rev.*, 1996, **96**, 443.
12. (a) L. Chao-Jun, *Chem. Rev.*, 2005, **105**, 3095; (b) D. Gryko, W. J. Saletra, O*rg. Biomol. Chem.*, 2007, **5**, 2148; (c) F. Giacalone, M. Gruttadauria, A. M. Marculescu, R. Noto, *Tetrahedron Lett.*, 2007, **48**, 255; (d) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (e) A. S. Kucherenko, D. E. Syutkin, S. G. Zlotin, *Russ. Chem. Bull.* (*Int. Ed.*), 2008, **57**, 591 [*Izv. Akad. Nauk, Ser. Khim.*, 2008, 578]; (f) D. E. Siyutkin, A. S. Kucherenko, S. G. Zlotin, *Tetrahedron*, 2010, **66**, 513; (g) D. E. Siyutkin, A. S. Kucherenko, L. L. Frolova, A. V. Kuchin, S. G. Zlotin, *Tetrahedron: Asymmetry*, 2011, **22**, 1320; (h) S. V. Kochetkov, A. S. Kucherenko, S. G. Zlotin, *Eur. J. Org. Chem.*, 2011, 6128; (i) S. V. Kochetkov, A. S. Kucherenko, G. V. Kryshtal, G. M. Zhdankina, S. G. Zlotin, *Eur. J. Org. Chem.*, 2012, 7129.
13. (a) M. K. Zhu, X. Y. Xu, L. Z. Gong, *Adv. Synth. Catal.*, 2008, **350**, 1390; (b) S. S. V. Ramasastry, K. Albertshofer, N. Utsami, C. F. Barbas III, *Org. Lett.*, 2008, **10**, 1621.
14. G. W. Anderson, J. Blodinger, R. W. Young, A. D. Welcher, *J. Am. Chem. Soc.*, 1952, **74**, 5304.
15. S. W. Fox, H. Wax, *J. Am. Chem. Soc.*, 1950, **72**, 5087.
16. J. Escorihuela, M. I. Burguete, S. V. Luis, *Tetrahedron Lett.*, 2008, **49**, 6885.

17. H. T. Hanson, E. L. Smith, *J. Biol. Chem.*, 1949, **179**, 815.
18. M. J. Liley, T. Johnson, S. E. Gibson, *J. Org. Chem.*, 2006, **71**, 1322.
19. B. Tortorella, G. Bettoni, *Gazz. Chim. Ital.*, 1968, **98**, 316.
20. J. C. Sheehan, B. M. Bloom, *J. Am. Chem. Soc.*, 1952, **74**, 3825.
21. T. Nemoto, T. Harada, T. Matsumoto, Y. Hamada, *Tetrahedron Lett.*, 2007, **48**, 6304.
22. F. Chen, S. Huang, H. Zhang, F. Liu, Y. Peng, *Tetrahedron*, 2008, **64**, 9585.
23. D. A. Evans, Y. Aye, J. Wu, *Org. Lett.*, 2006, **8**, 2071.
24. N. Basse, S. Piguel, D. Papapostolou, A. Ferrier-Berthelot, N. Richy, M. Pagano, P. Sarthou, J. Sobczak-Thepot, M. Reboud-Ravaux, J. Vidal, *J. Med. Chem.*, 2007, **50**, 2842.
25. E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2006, **45**, 7230.
26. H. Nitta, D. Yu, M. Kudo, A. Mori, S. Inoue, *J. Am. Chem. Soc.*, 1992, **114**, 7969.
27. Y. Xu, A. Cordova, *Chem. Commun.*, 2006, 460.
28. D. Font, C. Jimeno, M. A. Pericas, *Org. Lett.*, 2006, **8**, 20.
29. J. R. Chen, H. H. Lu, X. Y. Li, L. Cheng, J. Wan, W. J. Xiao, *Org. Lett.*, 2005, **7**, 20.

Received 25, December 2012