New bifunctional organocatalysts based on (*R*,*R*)-cyclohexane-1,2-diamine for the asymmetric addition of nucleophiles to aldehydes

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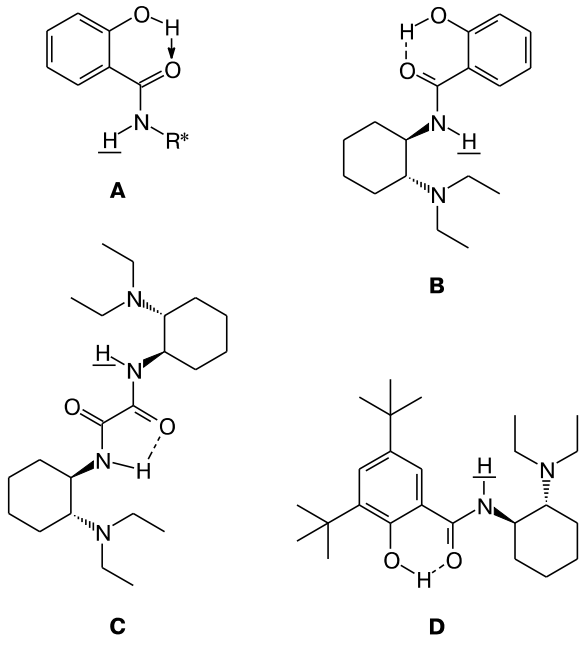
The amide and sulfamide derivatives of (1*R*,2*R*)-*N*,*N*-diethylcyclohexane-1,2-diamine can serve as organocatalysts for addition of Me_3SiCN and Et_2Zn to aldehydes.

Key words: organocatalysis, asymmetric synthesis, aldehydes, trimethylsilyl cyanide, diethylzinc, (*R*,*R*)-cyclohexane-1,2-diamine.

Bifunctional catalysts containing basic and acidic fragments evoke increasing interest in the recent time.[1,2] This is primarily related to their universal character, *viz.*, the ability to simultaneously activate the nucleophile and electrophile, and high potential of their use.[3—5] The scope of the main, most accessible and used compounds of this type bearing the chiral function is rather restricted and includes natural amino acids,[6,7] quinine and cinchonidine derivatives,[8,9] TADDOLs,[10—13] BINOL,[14—16] and cyclohexane-1,2-diamine derivatives.[17] The compounds combining the thiourea and cyclohexanediamine fragments, where the thiourea moiety is responsible for the acidic function and the free (or alkylated) amino group provides basicity, turned out to be most promising (and, hence, studied[18,19]). These chiral thioureas found wide use as organocatalysts in various reactions of C—C bond formation, for instance, in the dynamic kinetic cleavage of azalactones,[20] the reduction of ketones,[21] and the Michael reaction.[22]



Results and Discussion

Intramolecular activation by the Brønsted acid of the Brønsted acid ("Brønsted Acid Assisted Brønsted Acid Catalysts" (BBA)) is observed in salicylamides (**A**).[23] Due to hydrogen bonding of the phenolic proton with the oxygen atom of the amide residue, the acidity of the NH proton is enhanced (**B**—**D**, the H atoms with the increased acidity are underlined).

In this work, we synthesized the new monoamide derivatives of cyclohexane-1,2-diamine (Schemes 1 and 2) and studied their catalytic activity in the addition of nucleophiles to aldehydes, namely, trimethylsilylcyanation and the addition of diethylzinc to aromatic aldehydes. The products of these reactions are important intermediates for the preparation of diverse chiral derivatives.[24—26]

There are few examples for the trimethylsilylcyanation of carbonyl compounds using organocatalysts. One work can be emphasized, where the 97% *ee* of the product was attained in the reaction involving the bifunctional catalyst based on the thiourea derivative and cyclohexanediamine[27] in an amount of 5 mol.% at −78 °C. Many works[28] are devoted to the use of amino alcohols and amino amides as catalysts for diethylzinc addition to aldehydes. When the cyclohexanediamine derivative was used as a ligand in the titanium complex,[29] the reaction product was isolated in a yield of 78% and *ee* 99% at −20 °C.

(1*R*,2*R*)-*N*,*N*-Diethylcyclohexanediamine (**6**) synthesized by the modified procedure[30] (see Scheme 1) was chosen as the starting compound for the preparation of the catalysts.

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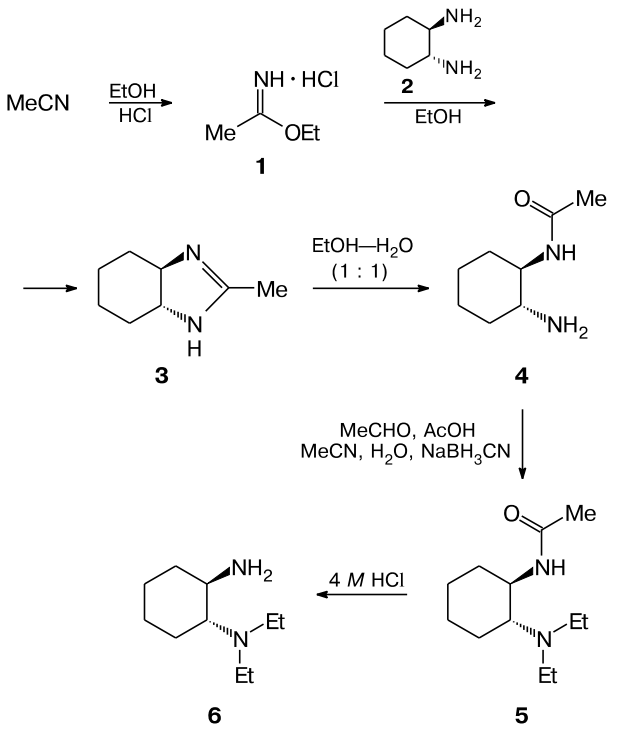
Scheme 1



Monoamide derivatives **7—10** based on compound **6** were synthesized according to Scheme 2 from the corresponding acids.

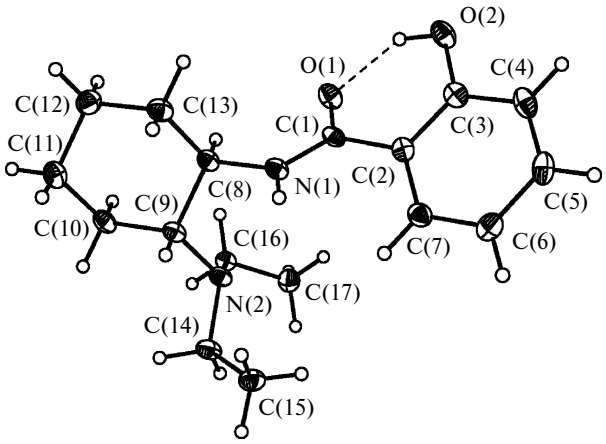


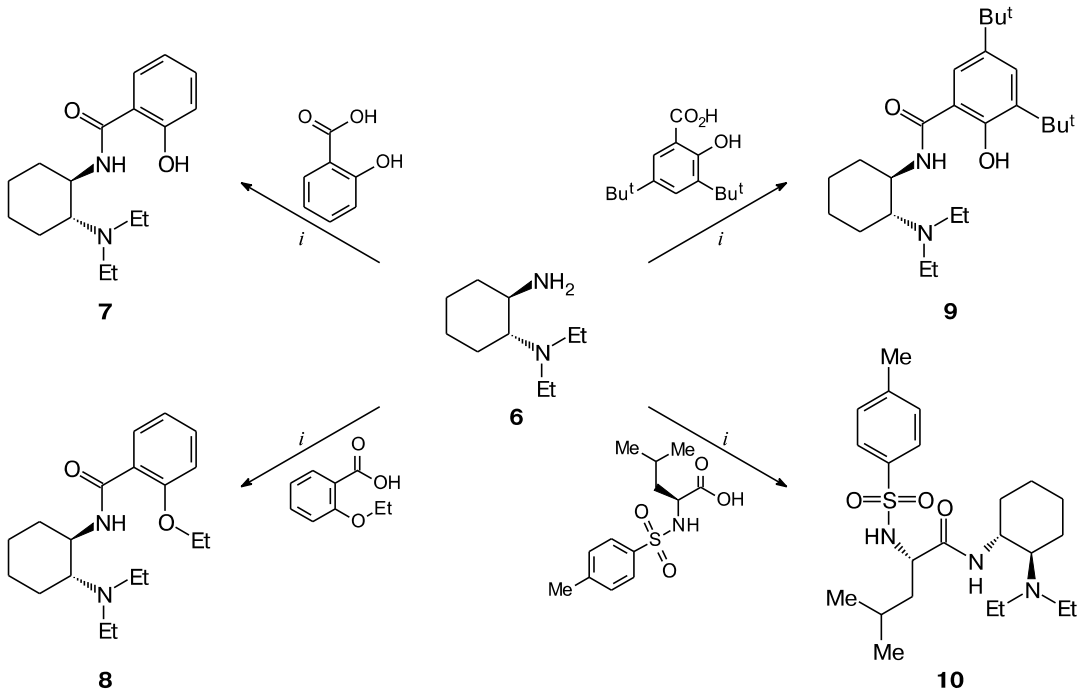
Fig. 1. Molecular structure of compound **7** (one of the two crystallographically independent molecules is shown). Dashed line is the intramolecular hydrogen bond.

The reaction of diamine **6** (2 equiv.) with oxalyl chloride in the presence of triethylamine affords oxalic acid derivative **11** in 70% yield (Scheme 3).

The structures and compositions of synthesized compounds **7—11** were confirmed by the elemental analysis and ^{1}H and ^{13}C spectroscopy data. The X-ray structure study was also carried out (Fig. 1, Tables 1 and 2).

Compound **7** crystallizes in the chiral space group $P2_1$ with two crystallographically independent molecules of similar geometry in the unit cell (Fig. 2).

Scheme 2



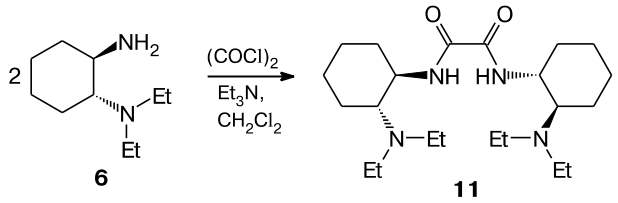
Conditions: *i*. DCC, CH_2Cl_2.

Table 1. Parameters of hydrogen bonds in structure **7**

D—H...A*	*d*/Å			Angle D—H—A /deg
	D—H	H...A	D...A	
N(1)—H(1)N...O(1) [$-x$, $y + 1/2$, $-z + 1$]	0.90	2.28	3.123(3)	156
O(2)—H(2)O...O(1)	0.92	1.79	2.612(3)	146
N(3)—H(3)N...O(3) [$-x + 2$, $y + 1/2$, $-z + 2$]	0.91	2.25	3.112(3)	158
O(4)—H(4)O...O(3)	0.94	1.79	2.638(3)	148

* D is proton donor, and A is proton acceptor.

Scheme 3



The structure of molecule **7** is determined to a substantial extent by both intra- and intermolecular hydrogen bonds (see Table 1). The angle between the amide and phenol fragments is 27.8 and 29.0°, respectively, for two crystallographically independent molecules. The nitrogen atom of the diethylamino group has a pyramidal coordination (the sum of the bond angles at the N(2) and N(4) nitrogen atom is 341.2 and 339.4°, respectively, for two crystallographically independent molecules).

In crystal the molecules of compound **7** are localized on the 2_1 axes and form the corresponding screw chains along the *b* axis due to the intermolecular hydrogen bonds N—H...O (Fig. 3, see Table 1). The chains are shifted relative to each other along the monoclinicity axis at a distance of ~0.25*b* according to the principle of closest packing, *i.e.*, "ledge-to-hollow." Similar shift of the chain along with the close geometry of two independent molecules determines the presence in the crystal structure of non-crystallographic symmetry pseudo-elements: the pseudo-center of inversion and the pseudo-plane of sliding reflection *c*, which are manifested, particularly, in systematic pseudo-quenchings of the corresponding reflections.

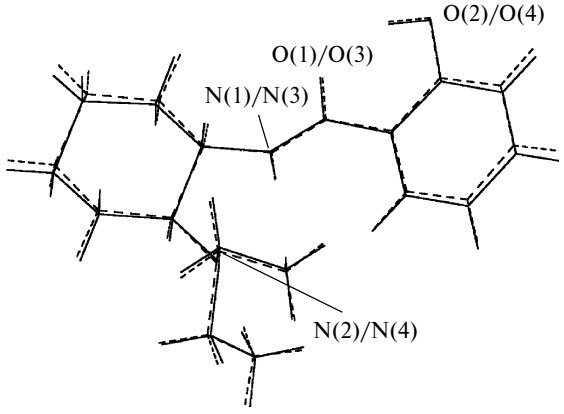


Fig. 2. Comparative geometry of two crystallographically independent molecules of compound **7**.

Table 2. Selected crystallographic data and refinement parameters for compound **7**

Parameter	Value
Empirical formula	$C_{17}H_{26}N_2O_2$
Molecular weight	290.40
T/K	100
Crystal size/mm	0.21×0.18×0.15
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	10.6662(5)
b/Å	9.5798(4)
c/Å	16.7038(8)
β/deg	108.391(1)
V/Å^3	1619.62(13)
Z	4
d_{calc}/g cm^{-3}	1.191
F(000)	632
μ/mm^{-1}	0.078
$2\theta_{max}$/deg	56
Number of measured reflections	18190
Number of independent reflections	4107
Number of observed reflections with $I > 2\sigma(I)$	2746
Number of refined parameters	383
R_1 ($I > 2\sigma(I)$)	0.038
wR_2 (all data)	0.095
Goodness-of-fit for F^2	1.001
T_{max}; T_{min}	0.988; 0.984

A molecule of compound **7** contains two asymmetric carbon atoms C(8) and C(9). Since structure **7** contains no atoms with $Z > 14$ (Si), the objective determination of the absolute configuration of these atoms is not possible. The relative configuration of these centers is 8*R**, 9*R**.

We assumed that compounds **7**—**11** would act as chiral bifunctional catalysts in the addition of trimethylsilyl cyanide (TMSCN) and Et_2Zn to benzaldehyde and, thus, would simultaneously activate the electrophilic and nucleophilic components.

In the trimethylsilylcyanation of benzaldehyde (Scheme 4), the use of catalysts **8** and **10** results in the formation of racemic products in quantitative yields. In the presence of catalysts **7** and **11**, the yield of the product was 99 and 63%, respectively, and enantiomeric enrichment was observed: 6% of the *R*-isomer in the case of catalyst **7** and 5% of the *S*-isomer in the case of catalyst **11**. Among

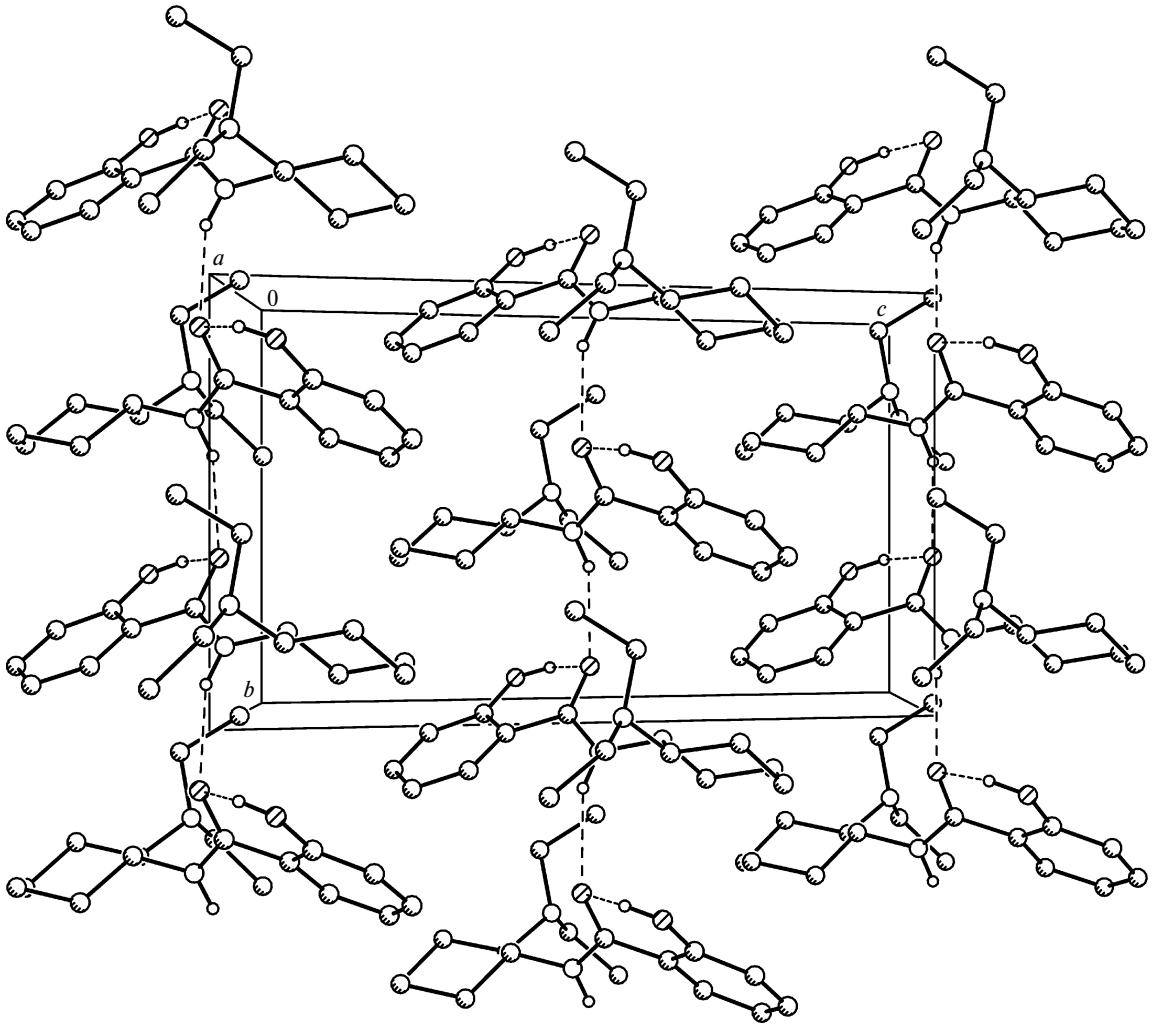
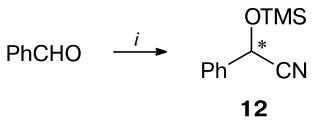


Fig. 3. Crystal structure of compound **7** in projection along the *a* axis. Dashed lines show hydrogen bonds.

all synthesized compounds, compound **9** exhibited the highest catalytic activity and, being taken in an amount of 5 mol.%, within 24 h in toluene provided the quantitative yield and enantiomeric enrichment of the reaction product with 20% of the *S*-isomer (Table 3). The reaction in dichloromethane decreased the yield of the product to 65%, and the enantioselectivity of the reaction to 16%.

Scheme 4



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i. TMSCN, catalyst,* ~20 °C, $PhCH_3$, 24 h.

When the amount of catalyst **9** is decreased to 1 and 0.5 mol.%, *O*-silylmandelonitrile **12** is formed in quantitative yield, and the enantioselectivity of the process is 6 and 5%, respectively. The further decrease in the catalyst amount to 0.1 mol.% results in a slight decrease in the reaction rate and enantiomeric excess of the product. Thus, it can be assumed that it is the presence of the bulky *tert*-butyl groups in compound **9** which restricts the number of possible positions of the substrate (TMSCN) relative to the catalyst and is responsible for enantioselectivity of the reaction.

For the addition of diethylzinc to benzaldehyde (Scheme 5, Table 4), the amounts of diethylzinc and the solvent were optimized using catalyst **9**. It was found that the yield of the product increases from 55 to 99% (see Table 4, entries *15—17*) with an increase in the amount of diethylzinc from 1.5 to 3 equiv. in toluene. In this case, the enantiomeric purity of the product ((*R*)-configuration) increases from 31 to 37%. When toluene and hexane are used as solvents, the reaction product is formed in quantitative yield; however, the enantiomeric excess of the product is considerably higher in the first case (37%

Table 3. Dependence of the yield and *ee* of product on the solvent and amount of the catalyst (*m*)*

Entry	Catalyst	*m* (mol.%)	Solvent	Product	
				Yield (%)	*ee* (%) (configuration)
1	**7**	0.5	Toluene	82	6 (*R*)
2	**7**	5	CH_2Cl_2	99	5 (*R*)
3	**8**	5	CH_2Cl_2	99	0
4	**9**	5	CH_2Cl_2	65	16 (*S*)
5	**10**	5	CH_2Cl_2	83	0
6	**11**	5	CH_2Cl_2	63	5 (*S*)
7	**9**	1	CH_2Cl_2	99	5 (*S*)
8	**9**	0.5	CH_2Cl_2	99	6 (*S*)
9	**9**	0.1	CH_2Cl_2	55	5 (*S*)
10	**9**	5	Toluene	80	20 (*S*)
11	**9**	5	Hexane	82	10 (*S*)
12	**9**	5	MeCN	98	15 (*S*)
13	**9**	5	THF	59	10 (*S*)

* Reaction conditions: benzaldehyde (0.05 mL, 0.47 mmol), trimethylsilyl cyanide (0.1 mL, 0.74 mmol), solvent (0.25 mL), argon, 25 °C, reaction time 24 h.

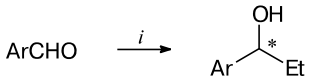
compared to 9%). When the reaction is carried out using catalysts **7**, **8**, and **10**, the reaction in toluene proceeds quantitatively; however, the products are racemic (entries *18* or *19*) or an insignificant enantiomeric enrichment of the product of 7% is observed (entry *14*). The use of catalyst **11** results in the predomination of (*S*)-configured enantiomer (entry *20*), and the maximum *ee* value of 62% was achieved during the reaction at −15 °C (entry *21*).

Table 4. Dependence of the yield and *ee* of the reaction product of diethylzinc addition to benzaldehyde on the catalyst type[a]

Entry	Catalyst	Amount of Et_2Zn (equiv.)	Product	
			Yield (%)	*ee* (%) (configuration)
14	**7**	3	99	7 (*R*)
15	**9**	3	99	37 (*R*)
16[b]	**9**	1.5	55	31 (*R*)
17[c]	**9**	3	99	9 (*R*)
18	**8**	3	77	0
19	**10**	3	90	0
20	**11**	3	99	34 (*S*)
21[b]	**11**	1.5	55	62 (*S*)

[a] Reaction conditions: catalyst (0.012 mmol), Et_2Zn (0.48 mmol), benzaldehyde (0.24 mmol), toluene (0.25 mL), 20 °C, argon, solvent toluene.
[b] Reaction temperature −15 °C, reaction time 72 h.
[c] Solvent hexane.

Scheme 5



13

i. Et_2Zn, catalyst,* ~20 °C, $PhCH_3$, 24 h, then H_3O^+.

The substrate specificity was studied under the optimum conditions using the most efficient catalysts **9** and **11**. As can be seen from Table 5, for catalyst **9** the introduction of halogen substituents into the *ortho*-position to the carbonyl group in the aldehyde molecule decreases the yield of the product. When using *o*-fluoro- and *o*-chlorobenzaldehydes, the enantiomeric excess of the product remains unchanged and is equal to 23%, whereas it is 19% *ee* for *o*-bromobenzaldehyde.

Probably, substituents in the *ortho*-position of benzaldehyde create steric hindrances for the interaction. The reaction with 2-naphthaldehyde occurs with the 88% yield and 30% enantioselectivity.

In summary, we synthesized new organocatalysts, which in an amount of 5 mol.% catalyze the addition of TMSCN and Et_2Zn to benzaldehydes. Although the maximum enantiomeric enrichment of *O*-trimethylsilylmandelonitrile was 20% and that of 1-phenylpropan-1-ol was 62%, it can be expected that the further modification of the catalyst structure (introduction of more bulky substituents in the benzene ring; in the case of catalyst **11**, the replacement of the oxalic acid residue by residues of other dicarboxylic acids) can substantial-

Table 5. Dependence of the yield and *ee* of the reaction product on the substituent in an aldehyde molecules using catalysts **9** and **11**[a]

Entry	Aldehyde	Catalyst	Product	
			Yield (%)	*ee* (%) (configuration)[b]
22	PhCHO	**9**	99	37 (*R*)
23[c]	PhCHO	**11**	55	62 (*S*)
24	PhCHO	**11**	99	34 (*S*)
25	2-$C_{10}H_7CHO$	**9**	88	30 (*N.D.*)
26	2-BrC_6H_4CHO	**9**	65	19 (*N.D.*)
27	2-BrC_6H_4CHO	**11**	42	13 (*N.D.*)
28	2-ClC_6H_4CHO	**9**	75	23 (*N.D.*)
29	2-ClC_6H_4CHO	**11**	93	35 (*N.D.*)
30	2-FC_6H_4CHO	**9**	93	23 (*N.D.*)
31	2-FC_6H_4CHO	**11**	46	10 (*N.D.*)

[a] Reaction conditions:: catalyst (0.012 mmol), Et_2Zn (0.48 mmol), aldehyde (0.24 mmol), toluene (0.25 mL), 20 °C, nitrogen.
[b] *N.D.* means that the absolute configuration of the predominant isomer was not determined.
[c] Reaction temperature −15 °C, reaction time 3 days.

ly enhance their catalytic activity and stereodifferentiating ability.

Experimental

^{1}H NMR spectra were recorded on Bruker Avance 300 (working frequency 300.13 MHz) and Bruker Avance 400 (working frequency 400.13 MHz) spectrometers. Chemical shifts were determined relative to the residual signal of the undeuterated solvent ($CDCl_3$ or DMSO-d_6); optical rotation was measured on a Perkin—Elmer 241 polarimeter in 0.1- or 0.5-dm cells temperature-maintained at 25 °C. Silica gel Kieselgel 60 (Merck) was used for column chromatography. Elemental analysis was carried out at the Laboratory of Elemental Analysis of the A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences. All solvents were purified according to standard procedures. Freshly distilled benzaldehyde and trimethylsilyl cyanide were used for the reactions.

Unit cell parameters and reflection intensities were measured on a Bruker SMART APEX-II CCD automated three-circle diffractometer (T = 100 K, λ(Mo-Kα) radiation, graphite monochromator, φ and ω scan modes). An X-ray absorption correction was applied by the SADABS program.[31] Selected crystallographic data are given in Table 2. The structure was solved by a direct method and refined by the least-squares full-matrix method in the anisotropic approximation for non-hydrogen atoms. The hydrogen atoms of the hydroxy and amino groups were objectively localized in difference Fourier syntheses and refined with fixed positional and thermal parameters. Positions of other hydrogen atoms were calculated geometrically and included into refinement with fixed positional (riding model) and thermal (U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups and U_{iso}(H) = 1.2U_{eq}(C) for all other groups) parameters. All calculations were performed using the SHELXTL program package.[32] The tables of atomic coordinates, bond lengths, bond angles, and anisotropic temperature parameters for compound **7** were deposited with the Cambridge Crystallographic Data Centre.

Enantiomeric analysis of the reaction products was carried out on a gas chromatograph using a PP-TFA-γ-CD capillary column (25×0.23 mm, film thickness 0.12 μm, column temperature 50 °C, gas N_2 (1.80 bar)). To carry out this analysis for 1-phenylpropan-1-ol, its trifluoroacetyl derivative was synthesized.

(1*R*,2*R*)-Cyclohexane-1,2-diamine was synthesized by the cleavage of the racemic sample to form the diastereomeric salt with (1*R*,2*R*)-tartaric acid[33] followed by the isolation of the free base by a known procedure.[34]

(3a*R*,7a*R*)-2-Methyl-3a,4,5,6,7,7a-hexahydro-1*H*-benz[*d*]-imidazole (3). Gaseous HCl was bubbled through a solution of anhydrous acetonitrile (1 mL, 19 mmol, 2.0 equiv.) and anhydrous ethanol (6 mL) for 1.5 h, after which the solution was evaporated. (1*R*,2*R*)-Cyclohexane-1,2-diamine (1.1 g, 9.6 mmol, 1 equiv.) was added as one portion to unpurified ethyl acetimidate hydrochloride dissolved in anhydrous ethanol, and the mixture was stirred for 8—10 h at ~20 °C. Then 1 *M* NaOH (aqueous, 75 mL) was added, and the product was extracted with 5% MeOH in CH_2Cl_2 (3×50 mL). The combined extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator. Compound **3** without additional purification was used at the next stage. The yield was 55%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.31 (s, 1 H); 2.94—2.92 (m, 2 H); 2.16 (d, 2 H, J = 11.6 Hz); 1.95 (s, 3 H); 1.78—1.76 (m, 2 H); 1.44—1.38 (m, 2 H); 1.31—1.25 (m, 2 H).

***N*-((1*R*,2*R*)-2-Aminocyclohexyl)acetamide (4).** Compound **3** (1.3 g, 8.3 mmol) was heated for 12 h in an ethanol—water (1 : 1) mixture, and then the solvent was removed on a rotary evaporator. The yield was 40%, $[\alpha]^{25}_D$ +10.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.05—1.28 (m, 4 H); 1.60—1.63 (m, 2 H); 1.74 (s, 3 H); 1.91—1.94 (m, 3 H); 3.38—3.47 (m, 1 H); 6.29 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 23.5, 25.0, 32.6, 35.5, 55.4, 56.0, 57.8, 170.6.

(1*R*,2*R*)-*N*,*N*-Diethylcyclohexane-1,2-diamine (6). A mixture of compound **4** (1.6 g, 10 mmol, 1 equiv.), acetaldehyde (2.85 mL, 50 mmol, 5 equiv.), water (3 mL), and acetonitrile (60 mL) was stirred for 15 min, then sodium cyanoborohydride (1.35 g, 21 mmol, 2.1 equiv.) was added, the mixture was stirred for 15 min, then acetic acid (4 mL) was added, and the mixture was stirred for 2 h. The solvent was removed on a rotary evaporator, and the residue was placed in a separating funnel with ethyl acetate (100 mL) and 1 *M* NaOH (50 mL). The organic layer was washed with 1 *M* NaOH (2×50 mL) and a solution of NaCl (50 mL), dried over Na_2SO_4, and then concentrated on a rotary evaporator. The residue was refluxed for 12 h with 4 *M* HCl (50 mL). The solution was cooled to ~20 °C and treated with 4 *M* NaOH to pH = 13. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and dried with Na_2SO_4. The solvent was removed on a rotary evaporator. The reaction product was obtained in 60% yield, $[\alpha]^{25}_D$ −110.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.98 (t, 6 H, J = 5.4 Hz); 1.21—1.05 (m, 4 H); 1.65—1.62 (m, 2 H); 1.75—1.71 (m, 2 H); 1.99—2.06 (m, 2 H); 2.35—2.27 (m, 2 H); 2.61—2.50 (m, 2 H).

***N*-((1*R*,2*R*)-2-Diethylaminocyclohexyl)-2-hydroxybenzamide (7).** A solution of salicylic acid (0.244 g, 1.76 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) and dicyclohexylcarbodiimide (0.436 g, 2.11 mmol, 1.2 equiv.) was added to a solution of compound **6** (0.3 g, 1.76 mmol, 1 equiv.) in a minimum amount of CH_2Cl_2. The reaction mixture was stirred for 24 h at ~20 °C, and the formed precipitate of dicyclohexylurea was filtered off. The mother liquor was concentrated on a rotary evaporator and purified by column chromatography (eluent ethyl acetate, R_f = 0.2). M.p. 82 °C, $[\alpha]^{25}_D$ −125.7 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ: 1.07 (t, 6 H, J = 7.2 Hz); 1.34—1.21 (m, 5 H); 1.75—1.70 (m, 1 H); 1.91—1.82 (m, 2 H); 2.45—2.33 (m, 2 H); 2.70—2.63 (m, 4 H); 3.59—3.53 (m, 1 H); 6.82 (t, 1 H, J = 7.8 Hz); 6.95 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 7.2 Hz); 7.42—7.31 (m, 2 H); 7.74 (br.s, 1 H). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.93 (t, 6 H, J = 7.2 Hz); 1.36—1.22 (m, 4 H); 1.70—1.67 (m, 1 H); 1.88—1.77 (m, 2 H); 2.06—2.03 (m, 1 H); 2.35—2.31 (m, 2 H); 2.58—2.49 (m, 4 H); 3.82 (br.s, 1 H); 6.84—6.80 (m, 2 H); 7.34—7.29 (m, 1 H); 7.77 (d, 1 H, J = 7.6 Hz); 8.24 (br.s, 1 H). Found (%): C, 70.18; H, 9.04; N, 9.41. $C_{17}H_{26}N_2O_2$. Calculated (%): C, 70.31; H, 9.02; N, 9.65.

3,5-Di-*tert*-butyl-*N*-((1*R*,2*R*)-2-diethylaminocyclohexyl)-2-hydroxybenzamide (9). A solution of 3,5-di-*tert*-butylsalicylic acid (0.399 g, 1.76 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) and dicyclohexylcarbodiimide (0.436 g, 2.11 mmol, 1.2 equiv.) was added to a solution of compound **6** (0.3 g, 1.76 mmol, 1 equiv.) in a minimum amount of CH_2Cl_2. The reaction mixture was stirred for 24 h at ~20 °C, and the precipitate of dicyclohexylurea that formed was filtered off. The mother liquor was concentrated on a rotary evaporator and purified by column chromatography (eluent toluene—ethyl acetate (1 : 4), R_f = 0.7). M.p. 152 °C,

$[\alpha]^{25}_D$ −57.3 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDC1_3$), δ: 1.07 (t, 6 H, *J* = 6.9 Hz); 1.29 (s, 9 H); 1.42 (s, 9 H); 1.74—1.67 (m, 3 H); 1.97—1.83 (m, 4 H); 2.42—2.31 (m, 2 H); 2.64—2.53 (m, 3 H); 2.85—2.81 (d, 1 H, *J* = 11.4 Hz); 3.48—3.43 (m, 2 H); 7.26 (s, 1 H); 7.42 (d, 1 H, *J* = 2.4 Hz). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.26 (c, 9 H); 1.31—1.30 (m, 3 H); 1.35 (c, 9 H); 1.73—1.58 (m, 9 H); 1.95—1.91 (m, 1 H); 2.31—2.28 (m, 2 H); 2.56—2.53 (m, 3 H); 3.90 (br.s, 1 H); 5.59 (d, 1 H, *J* = 8.1 Hz); 7.33 (d, 1 H, *J* = 2.1 Hz); 7.55 (d, 1 H, *J* = 2.1 Hz); 8.25 (br.s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 23.46, 24.56, 24.97, 25.62, 25.82, 29.39, 31.36, 32.16, 33.97, 34.27, 35.16, 42.99, 49.10, 51.54, 63.12, 113.79, 119.63, 128.27, 137.82, 139.51, 158.84, 171.82. Found (%): C, 74.48; H, 10.49; N, 7.00. $C_{25}H_{42}N_2O_2$. Calculated (%): C, 74.58; H, 10.51; N, 6.96.

***N*-((1*R*,2*R*)-2-Diethylaminocyclohexyl)-2-ethoxybenzamide (8).** A solution of 2-ethoxybenzoic acid (0.292 g, 1.76 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) and dicyclohexylcarbodiimide (0.436 g, 2.11 mmol, 1.2 equiv.) was added to a solution of diamine **6** (0.3 g, 1.76 mmol, 1 equiv.) in a minimum amount of CH_2Cl_2. The reaction mixture was stirred for 24 h at ~20 °C, and the precipitate of dicyclohexylurea that formed was filtered off. The mother liquor was concentrated on a rotary evaporator and purified by column chromatography (eluent toluene—ethyl acetate (1 : 3), R_f = 0.3), $[\alpha]^{25}_D$ −72.5 (*c* 1, MeOH). ^{1}H NMR (300 MHz, $CDC1_3$), δ: 1.00 (t, 6 H, *J* = 7.8 Hz); 1.24—1.09 (m, 6 H); 1.50 (t, 3 H, *J* = 6.9 Hz); 1.70—1.66 (m, 1 H); 1.82—1.79 (m, 1 H); 1.89—1.86 (m, 1 H); 2.38—2.31 (m, 2 H); 2.70—2.56 (m, 2 H); 3.89—3.79 (m, 2 H); 6.95 (d, 1 H, *J* = 8.4 Hz); 7.06 (t, 1 H, *J* = 7.8 Hz); 7.41—7.35 (m, 1 H); 8.20—8.17 (m, 1 H); 8.30 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.49, 14.77, 23.98, 24.95, 25.76, 33.26, 43.21, 48.63, 48.76, 51.63, 55.06, 62.69, 64.15, 64.43, 66.11, 112.32, 120.92, 132.17. Found (%): C, 71.59; H, 9.49; N, 8.78. $C_{19}H_{30}N_2O_2$. Calculated (%): C, 71.66; H, 9.50; N, 8.80.

***N*,*N*′-Bis((*R*,*R*)-2-diethylaminocyclohexyl)oxalylamide (11).** Diamine **6** (0.2 g, 1.17 mmol, 2 equiv.) was dissolved in a minimum amount of CH_2Cl_2, the solution was cooled to 0 °C, and triethylamine (0.163 mL, 1.17 mmol, 1 equiv.) was added. A solution of oxalyl chloride (0.069 g, 0.59 mmol, 1 equiv.) in CH_2Cl_2 (12 mL) was slowly added dropwise to the reaction mixture on stirring, and the mixture was stirred for 16 h at 0 °C. The solvent was removed on a rotary evaporator, water was added, and the organics was extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and purified by column chromatography (eluent toluene—ethyl acetate (1 : 2), R_f = 0.4). M.p. 144 °C, $[\alpha]^{25}_D$ −89 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDC1_3$), δ: 0.97 (t, 12 H, *J* = 6.9 Hz); 1.21—1.15 (m, 8 H); 1.67—1.63 (m, 2 H); 1.82—1.73 (m, 4 H); 2.38—2.22 (m, 5 H); 2.58—2.41 (m, 7 H); 3.45—3.38 (m, 2 H); 7.98 (br.s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.81, 23.86, 24.69, 25.61, 29.71, 31.97, 43.21, 51.29, 62.80, 70.55, 160.17. Found (%): C, 66.90; H, 10.69; N, 14,12. $C_{22}H_{42}N_4O_2$. Calculated (%): C, 66.96; H, 10.73; N, 14.20.

(*S*)-*N*-((1*R*,2*R*)-2-Diethylaminocyclohexyl)-4-methyl-2-(4-methylphenylsulfonamino)pentanamide (10). A solution of *N*-tosylvaline (0.477 g, 1.76 mmol, 1 equiv.) in dichoromethane (1 mL) and dicyclohexylcarbodiimide (0.436 g, 2.11 mmol, 1.2 equiv.) was added to a solution of diamine **6** (0.3 g, 1.76 mmol, 1 equiv.) in a minimum amount of dichloromethane. The reaction mixture was stirred for 24 h at ~20 °C, and the precipitate of dicyclohexylurea that formed was filtered off. The mother liquor was concentrated on a rotary evaporator and purified by column chromatography (eluent toluene—ethyl acetate (3 : 1), R_f = 0.3). M.p. 83 °C, $[\alpha]^{25}_D$ −36.3 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDC1_3$), δ: 0.82 (d, 3 H, *J* = 6.6 Hz); 0.88 (d, 3 H, *J* = 6.6 Hz); 0.97 (br.s, 6 H); 1.24—1.14 (m, 5 H); 1.65—1.61 (m, 2 H); 1.82—1.76 (m, 3 H); 2.08—2.02 (m, 1 H); 2.38 (s, 3 H); 2.34—2.32 (m, 2 H); 2.46—2.45 (m, 1 H); 2.59—2.54 (m, 2 H); 3.31 (br.s, 1 H); 3.53 (d, 1 H, *J* = 4.2 Hz); 7.23 (d, 2 H, *J* = 7.7 Hz); 7.74 (d, 2 H, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.15, 17.30, 18.93, 21.52, 23.45, 24.40, 24.97, 25.51, 31.96, 43.14, 50.15, 50.79, 61.73, 62.55, 127.25, 129.61, 136.90, 143.35, 169.97, 178.36.

Addition of TMSCN to benzaldehyde. A 5-mL two-necked flask was heated to 200 °C, evacuated, filled with argon, and then cooled to ~20 °C. The flask was loaded under argon with a catalyst (5 mol.%), CH_2Cl_2, (0.25 mL), benzaldehyde (0.05 mL, 0.47 mmol), and TMSCN (0.1 mL, 0.74 mmol). The reaction mixture was stirred for 24 h under argon at ~20 °C and passed through a small layer (*d* = 0.5 cm, *h* = 2 cm) of silica gel to separate the catalyst, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy (no signals of other products were observed in the spectrum). ^{1}H NMR ($CDCl_3$) for trimethylsilyl mandelonitrile ether (**12**), δ: 7.49—7.39 (m, 5 H); 5.36 (s, 1 H); 0.24 (s, 9 H) (*cf.* Ref. 35).

Addition of diethylzinc to aldehydes. Diethylzinc (2 equiv., 0.48 mmol, 0.3 mL) was slowly added at 0 °C under argon to a solution of the catalyst (0.012 mmol) in toluene (0.25 mL). The reaction mixture was stirred, bringing the temperature to ~20 °C for 30 min, and then aldehyde (0.24 mmol) was added at the temperature indicated in Table 5. The mixture was stirred for 24 h. Then 1 *M* HCl was added, and the organics were extracted with dichloromethane (3×15 mL). The organic layer was concentrated on a rotary evaporator. 1-Arylpropan-1-ol that formed was purified by TLC on SiO_2 (eluent dichloromethane) (*cf.* Ref. 36).

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