Novel C_2-symmetric phenylglycine derivatives as organocatalysts of the Michael reaction between nitroalkenes and ketones*

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A comprehensive study of the activity of the amide-type organocatalysts based on (*R*)- and (*S*)-phenylglycine and 1,2-di(2-pyridyl)-1,2-diaminoethane in the asymmetric Michael reaction between various nitroalkenes and ketones was carried out. The products of the studied reactions were formed in up to 99% yield, with *syn* diastereoselectivity (*dr*) >20 : 1 and enantiomeric excess of up to 93% *ee* for *syn*-isomer. The organocatalysts can be regenerated and reused in at least seven reaction cycles.

Key words: asymmetric catalysis, organocatalysis, phenylglycine, Michael reaction, green chemistry, biologically active compounds.

In recent years, asymmetric organocatalysis has been increasingly used to design complex chiral compounds.[1—7] An important direction in this field of chemistry is the development of new catalysts based on small organic molecules.[8—10] The Michael reaction is one of the most efficient and powerful synthetic tools for the stereoselective formation of new carbon—carbon bonds.[11—13] Nitro olefins are widely used as Michael acceptors in the reactions with CH acids, since the resulting chiral γ-nitro carbonyl compounds can serve as universal precursors for the construction of more complex chiral biologically active compounds.[14] Earlier,[15,16] we have synthesized organocatalysts based on proline and its derivatives (substituted pyrrolidines, *etc.*), which have proved to be efficient in the asymmetric Michael reaction between nitro olefins and various aldehydes and ketones. Amino acids and their derivatives containing a primary amino group, which form the basis for enzymatic catalysis in living systems, are very attractive as catalysts.[17—19] Chiral derivatives of primary amino acids, and especially C_2-symmetric ones, have been poorly studied as organocatalysts of asymmetric Michael reactions, meanwhile, they can serve as efficient "donors of chirality" in some other asymmetric processes.[20—23] The introduction of fragments of chiral pyridine-containing diamines into amino acids often increases the activity and selectivity of catalysts, as well as prolongs their active period.[23] The present study is aimed at discovering the potential of catalysts typified by primary amines in the reactions between nitrostyrenes and ketones.

* Dedicated to Academician of the Russian Academy of Sciences V. N. Charushin on the occasion of his 70th birthday.

Results and Discussion

As the sources of chirality, we chose a sterically hindered amino acid phenylglycine in both enantiomeric forms. Diastereoisomeric organocatalysts **I** and **II** were synthesized in two steps from commercially available *N*-benzyloxycarbonyl-2-phenylglycines **1** and heterocyclic (*S*,*S*)-1,2-di(2-pyridyl)-1,2-diaminoethane **2** we obtained earlier.[23] In the first step, diaminoethane **2** was acylated with *N*-benzyloxycarbonyl-2-phenylglycines **1** using ethyl chloroformate in THF. In the second step, the protective groups were removed by catalytic hydrogenation in the presence of 5% Pd/C, which gave the corresponding amido amines **I** and **II** as white powders in high overall yields (81—85%) (Scheme 1).

The catalytic efficiency of the thus obtained C_2-symmetric primary amido amines **I** and **II** was tested in a model Michael reaction between nitrostyrene **3a** and cyclohexanone **4a** (Scheme 2, Table 1).

The highest activity and enantioselectivity in the model reaction between compounds **3a** and **4a** was exhibited by amide organocatalyst **I** based on (1*S*,2*S*)-1,2-di(2-pyridyl)-ethane-1,2-diamine and (*S*)-phenylglycine. The highest yield (85%) and enantiomeric excess (up to 92% *ee*) of product **5a** were achieved when the solvent-free reaction was carried out at 0 °C in the presence of 15 mol.% of the catalyst (Table 1, entry *9*). The use of organic solvents proved to be inefficient. A decrease in the amount of catalyst **I** to 5 mol.% (entries *10* and *11*) had an insignificant effect on the reaction enantioselectivity, with the yield of product **5a** markedly decreasing.

Organocatalyst **I** (15 mol.%, neat, 0 °C) showing the highest yield and enantioselectivity was used further to

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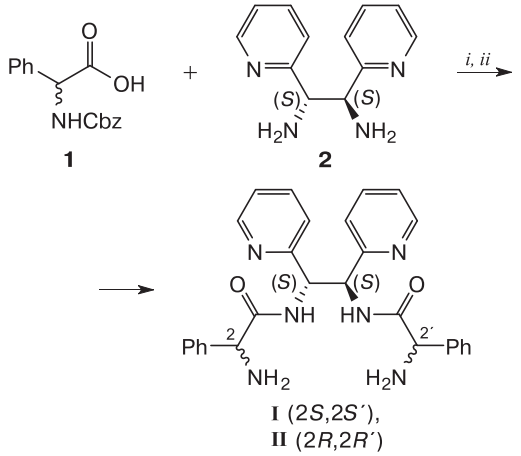
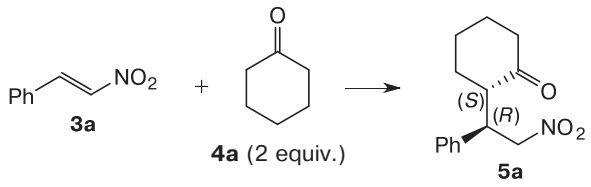
Scheme 1



Reagents and conditions: *i*. $ClCO_2Et$, Et_3N, THF, ~20 °C, 24 h; *ii*. H_2 (1 atm.), 5% Pd/C, MeOH, 5 h.

Scheme 2



Reagents and conditions: catalyst **I** or **II**, solvent, 24 h.

carry out reactions between various nitrostyrenes and cyclic and linear ketones (Scheme 3, Table 2). The reaction between cyclopentanone **4b** and nitrostyrene **3a** gave product **5b** (*dr syn* : *anti* = 7 : 1) in high yield (99%) and *syn*-enantioselectivity (90% *ee*) (see Table 2, entry *2*). The reaction of nitrostyrene **3a** with methyl ethyl ketone **4c** proceeded regioselectively at the methylene group to give branched product **5c** in moderate yield (55%) and enantiomeric excess (78% *ee*) (entry *3*). Acetone (**4d**) readily reacts with nitro olefin **3b** to form adduct **5d** in moderate yield (61%) and high enantioselectivity (89% *ee*) (see Table 2, entry *4*). Aromatic nitro olefins **3** containing halogen atoms (entries *4*—*6*) or a nitro group in the aromatic ring (entry *8*) can also be involved into the reaction (66—79% yields, 80—87% *ee*).

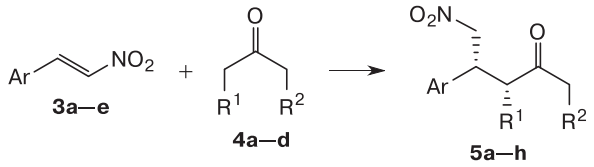
We have developed a procedure for the regeneration of organocatalyst **I** (Table 3). Thus, trifluoroacetic acid was added to the solution after the reaction completion, the mixture was stirred for 30 min and concentrated, product **5a** and unreacted starting compounds were extracted with diethyl ether. The organic layer was decanted, the trifluoroacetate salt of catalyst **I** was treated with Et_3N, washed with water, and vacuum dried. The regenerated

Table 1. Optimization of the conditions of the model reaction between nitrostyrene **3a** and cyclohexanone **4a**[a]

Entry	*T*/°C	Catalyst (mol.%)	Solvent	Yield[b,c] of **5a** (%)	*ee*[d] (%)
1	~20	**I** (15)	—[e]	85	84
2	~20	**II** (15)	—[e]	76	62[f]
3	~20	**I** (15)	PhMe	69	60
4	~20	**I** (15)	CH_2Cl_2	88	67
5	~20	**I** (15)	EtOAc	80	59
6	~20	**I** (15)	ТГФ	84	60
7	~20	**I** (15)	EtOH	90	63
8	~20	**I** (15)	Pr^iOH	87	67
9	0	**I** (15)	—[e]	82	92
10	0	**I** (10)	—[e]	70	91
11	0	**I** (5)	—[e]	55	88

[a] Reaction conditions: catalyst **I** or **II** (5—15 mol.%), nitrostyrene **3a** (7.5 mg, 0.05 mmol), cyclohexanone **4a** (9.8 mg, 0.1 mmol), solvent (0.1 mL) or neat, 24 h, ~20 °C.
[b] The yield of *syn*-**5a** after flash chromatography on silica gel.
[c] Diastereomeric ratio of *syn* : *anti* > 20 : 1 (^{1}H NMR spectral data).
[d] Enantiomeric excess was determined by HPLC on a Chiralpak AD-H chiral phase, the (1*R*,2*S*)-configuration of product **5a** was confirmed by comparing the rotation angle with the literature data.[11]
[e] Solvent-free.
[f] (1*S*,2*R*)-**5a** was obtained.

Scheme 3



3a—c: Ar = Ph (**a**), 3-ClC_6H_4 (**b**), 2-BrC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**)

4a—d: $R^1 + R^2 = (CH_3)_2$ (**a**), $(CH_2)_2$ (**b**); R^1 = H, R^2 = Me (**c**), H (**d**)

Compounds **5**	Ar	R^1	R^2
a	Ph	—$(CH_2)_3$—	
b	Ph	—$(CH_2)_2$—	
c	Ph	Me	H
d	3-ClC_6H_4	H	H
e	3-ClC_6H_4	—$(CH_2)_3$—	
f	2-BrC_6H_4	—$(CH_2)_3$—	
g	4-$MeOC_6H_4$	—$(CH_2)_3$—	
h	4-$O_2NC_6H_4$	—$(CH_2)_3$—	

Reagents and conditions: catalyst **I** (15 mol.%), neat, 0 °C, 24 h.

catalyst was used in the following cycles. After seven regenerations of catalyst **I**, its structure did not change (^{1}H NMR data). An increase in the reaction time during the seventh cycle is apparently associated with mechanical losses of the catalyst in the regeneration process (about 30% by weight after the seventh cycle).

Table 2. Scope of application of organocatalyst **I**[a]

Entry	Nitrostyrene **3**	Ketone **4**	Product	Yield[b,c] of **5** (%)	*ee*[d] *(syn)* **5** (%)
1	**3a**	**4a**	**5a**	85	84
2	**3a**	**4b**	**5b**	99[e]	90
3	**3a**	**4c**	**5c**	55	78
4	**3b**	**4d**	**5d**	61	89
5	**3b**	**4a**	**5e**	75	88
6	**3c**	**4a**	**5f**	79	85
7	**3d**	**4a**	**5g**	66	82
8	**3e**	**4a**	**5h**	70	93

[a] Reaction conditions: catalyst **I** (3.6 mg, 0.0075 mmol, 15 mol.%), nitrostyrene **3** (0.05 mmol), ketone **4** (0.1 mmol), 0 °C, 24 h.
[b] The yield of *syn*-**5** after flash chromatography on silica gel.
[c] Diastereomeric ratio of *syn* : *anti* > 20 : 1 (^{1}H NMR spectral data).
[d] Enantiomeric excess was determined by HPLC on Chiralpak AD-H, AS-H, and OD-H chiral phases.
[e] The ratio of *syn* : *anti* = 7 : 1.

Table 3. Regeneration of catalyst **I** in the reaction between compounds **3a** and **4a**[a]

Cycle	Yield of **5a** (%)	*ee* of **5a** (%)
1	82	92
2	80	92
3	79	91
4	78	90
5	75	87
6	71	83
7[b]	65	75

[a] Reaction conditions: catalyst **I** (36.0 mg, 0.075 mmol, 15 mol.%), nitrostyrene **3a** (74.5 mg, 0.5 mmol), cyclohexanone **4a** (98.0 mg, 1.0 mmol), 0 °C, 24 h.
[b] Reaction time 30 h.

The products of Michael reactions **5** between ketones **4** and β-nitrostyrene derivatives **3** can be used in the synthesis of enantiomerically enriched drugs. For example, product **5g** can be converted in several steps into the antidepressant (−)-venlafaxine (trade name Effexor).[24]

In conclusion, we have obtained a new efficient C_2-symmetric organocatalyst based on the amino acid (*S*)-phenylglycine and (*S*,*S*)-1,2-di(2-pyridyl)-1,2-diaminoethane. It was found to be efficient in the solvent-free Michael reaction between nitroalkenes and various cyclic and acyclic ketones. The products were formed in high yields (up to 99%), diastereo- (>20 : 1) and enantioselectivity for the *syn*-isomer (up to 93% *ee*). The compounds obtained can find application in the synthesis of chiral enantiomerically pure drugs. A procedure for the regeneration of organocatalysts based on primary amines has been developed, which ensures their multiple (at least seven cycles) use.

Experimental

We used commercially available reagents (Sigma-Aldrich Co.). Solvents were purified according to standard procedures. The starting nitroolefins **3** were synthesized according to the known procedures.[25] Column chromatography was performed on silica gel (Aldrich, 0.060—0.200 μm), the eluent was hexane—ethyl acetate (2 : 1 or 1 : 1). ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Bruker AM-300 spectrometer (300 MHz (^{1}H) and 75 MHz (^{13}C). High-resolution mass spectra were obtained on a Bruker microTOF II instrument. The enantiomeric composition of compounds **5a—h** was analyzed on a Styer high performance liquid chromatograph with a UV detector (220—254 nm) on stationary chiral phases (Chiralpak AD-H, AS-H, and OD-H, a 25-cm column). The rotation angles were determined on a Jasco P-2000 polarimeter.

Synthesis of catalysts I and II (general procedure). Triethylamine (0.66 mL) was added to a solution of (*R*)- or (*S*)-*N*-benzyloxycarbonyl-2-phenylglycine **1** (1.2 g, 4.68 mmol) in anhydrous THF (10 mL). Then, ethyl chloroformate (446.0 μL, 0.508 g, 4.68 mmol) was added slowly dropwise to the mixture, which was stirred for 30 min, followed by the addition of diamine **2** (0.5 g, 2.34 mmol). The reaction mixture was stirred for 24 h. The formed precipitate was filtered off, the filtrate was dried with $MgSO_4$, the solvent was evaporated on a rotary evaporator. The residue was dissolved in methanol (10 mL), 5% Pd/C (100 mg) was added, and the mixture was stirred for 5 h in an H_2 atmosphere (1 atm.). The reaction mixture was filtered, the filtrate was concentrated to obtain products **I** and **II** as white high-melting powders.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Di(2-pyridyl)ethane-1,2-diyl]-bis(2-amino-2-phenylacetamide) (I). The yield was 0.95 g (85%), a white powder. M.p. >230 °C. ^{1}H NMR (DMSO-d_6), δ: 4.87 (s, 2 H); 5.11 (br.s, 4 H); 5.85 (s, 2 H); 7.21—7.35 (m, 12 H); 7.50 (m, 2 H); 7.77 (m, 2 H); 8.01 (s, 2 H); 8.50 (m, 2 H). ^{13}C NMR (DMSO-d_6), δ: 57.3, 58.0, 121.1, 127.6, 129.1, 129.3 134.0, 144.3, 157.2, 170.1. Found: *m*/*z* 481.5685 $[M + H]^+$. Calculated for $C_{28}H_{29}N_6O_2$: 481.5683.

(2*R*,2′*R*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Di(2-pyridyl)ethane-1,2-diyl]-bis(2-amino-2-phenylacetamide) (II). The yield was 0.91 g (81%), a white powder. M.p. >230 °C. ^{1}H NMR (DMSO-d_6), δ: 4.84 (s, 2 H); 5.13 (br.s, 4 H); 5.86 (s, 2 H); 7.22—7.36 (m, 12 H); 7.49 (m, 2 H); 7.75 (m, 2 H); 8.03 (s, 2 H); 8.51 (m, 2 H). ^{13}C NMR (DMSO-d_6), δ: 57.3, 58.1, 121.0, 127.8, 129.3, 129.5 134.1, 144.3, 157.1, 170.0. Found: *m*/*z* 481.5687 $[M + H]^+$. Calculated for $C_{28}H_{29}N_6O_2$: 481.5683.

Catalytic Michael reaction between compounds 3 and 4 (general procedure). A corresponding ketone **4** (2 equiv., 0.1 mmol) was added to a mixture of organocatalyst **I** or **II** (3.6 mg, 0.0075 mmol, 15 mol.%) and nitrostyrene **3** (0.05 mmol), and the mixture was stirred for 24 h at the temperature indicated in Table 1 (optimization of conditions) or at 0 °C (synthesis of compounds **5b—h**). The solvent was evaporated, the residue was extracted with diethyl ether (3×4 mL) and purified by flash chromatography on silica gel (eluent hexane—ethyl acetate, 2 : 1 or 1 : 1). The spectral data for compounds **5b—h** correspond to those published earlier.[26]

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (5a). The yield was 10.1 mg (82%), a white powder. M.p. 124—126 °C, $[\alpha]_D^{20}$ −29.6 (*c* 0.1, $CHCl_3$), 92% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.10—1.22 (m, 1 H); 1.47—1.73 (m, 4 H); 1.98—2.04 (m, 1 H);

2.26—2.44 (m, 2 H); 2.61 (m, 1 H); 3.69 (dt, 1 H, J_1 = 9.9 Hz, J_2 = 4.5 Hz); 4.56 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 9.9 Hz); 4.87 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 4.5 Hz); 7.08—7.11 (m, 2 H); 7.19—7.27 (m, 3 H). Found: *m/z* 248.1284 $[M + H]^+$. Calculated for $C_{14}H_{18}NO_3$: 248.1281. The enantiomeric excess was determined on a Diacel Chiralpak AD-H stationary chiral phase at 254 nm (hexane—propan-2-ol (85 : 15), 1.0 mL min^{-1}; $t_{(R)}$ = 8.69 min (minor), 10.54 min (major)).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclopentanone (5b). A 7 : 1 mixture of *syn*- and *anti*-diastereomers. The yield was 11.7 mg (99%), a white powder. *syn*-Isomer 90% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.43—1.52 (m, 1 H); 1.68—1.75 (m, 1 H); 1.85—1.96 (m, 2 H); 2.08—2.18 (m, 1 H); 2.32—2.43 (m, 1.73 H, *syn*); 2.49—2.55 (m, 0.27 H, *anti*); 3.66—3.72 (m, 0.89 H, *syn*); 3.82—3.85 (m, 0.17 H, *anti*); 4.71 (dd, 1 H, J_1 = 12.8 Hz, J_2 = 10.0 Hz); 5.02 (d, 1 H, J = 7.62 Hz); 5.34 (dd, 1 H, J_1 = 12.8 Hz, J_2 = 5.6 Hz); 7.15—7.19 (m, 2 H); 7.28—7.34 (m, 3 H). Found: *m/z* 234.1124 $[M + H]^+$. Calculated for $C_{13}H_{16}NO_3$: 234.1125. The enantiomeric excess was determined on a Diacel Chiralpak AD-H stationary chiral phase at 220 nm (hexane—propan-2-ol (95 : 5), 1.0 mL min^{-1}; $t_{(R)}$ = 12.29 min (major, *anti*), 14.20 min (minor, *anti*), 15.87 min (minor, *syn*), 87.00 min (major, *syn*)).

(3*S*,4*R*)-3-Methyl-5-nitro-4-phenylpentan-2-one (5c). The yield was 6.1 mg (55%), a colorless oil, $[\alpha]_D^{20}$ −34.1 (*c* 0.1, $CHCl_3$), 78% *ee*. ^{1}H NMR ($CDCl_3$), δ: 0.93 (d, 3 H, J = 7.2 Hz); 2.15 (s, 3 H); 2.89—2.94 (m, 1 H); 3.59 (dt, 1 H, J_1 = 9.3 Hz, J_2 = 4.8 Hz); 4.48—4.61 (m, 2 H); 7.05—7.08 (m, 2 H); 7.18—7.27 (m, 3 H). Found: *m/z* 222.1121 $[M + H]^+$. Calculated for $C_{12}H_{16}NO_3$: 222.1125. The enantiomeric excess was determined on a Diacel Chiralpak AS-H stationary chiral phase at 220 nm (hexane—propan-2-ol (90 : 10), 0.5 mL min^{-1}; $t_{(R)}$ = 14.90 min (minor), 16.20 min (major)).

(*R*)-4-(3-Chlorophenyl)-5-nitropentan-2-one (5d). The yield was 7.4 mg (61%), a colorless oil, $[\alpha]_D^{20}$ −5.1 (*c* 0.1, $CHCl_3$), 89% *ee*. ^{1}H NMR ($CDCl_3$), δ: 2.05 (s, 3 H); 2.84 (d, 2 H, J = 6.9 Hz); 4.00 (d, 1 H, J = 5.6 Hz); 4.60 (dd, 1 H, J_1 = 9.0 Hz, J_2 = 5.7 Hz); 4.68 (dd, 1 H, J_1 = 7.0 Hz, J_2 = 5.0 Hz); 7.22—7.34 (m, 5 H). Found: *m/z* 242.0575 $[M + H]^+$. Calculated for $C_{11}H_{13}ClNO_3$: 242.0578. The enantiomeric excess was determined on a Diacel Chiralpak AS-H stationary chiral phase at 220 nm (hexane—propan-2-ol (85 : 15), 1.0 mL min^{-1}; $t_{(R)}$ = 21.76 min (minor), 29.79 min (major)).

(*S*)-2-[(*R*)-1-(3-Chlorophenyl)-2-nitroethyl]cyclohexanone (5e). The yield was 10.5 mg (75%), a brownish oil, 88% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.08—1.24 (m, 1 H); 1.45—1.72 (m, 4 H); 1.93—1.96 (m, 1 H); 2.19—2.36 (m, 2 H); 2.52—2.65 (m, 1 H); 3.67 (dt, 1 H, J_1 = 9.9 Hz, J_2 = 4.5 Hz); 4.52 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 9.9 Hz); 4.83 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 4.5 Hz); 6.96—7.01 (m, 1 H); 7.08 (s, 1 H); 7.12—7.20 (m, 2 H). Found: *m/z* 282.0889 $[M + H]^+$. Calculated for $C_{14}H_{17}ClNO_3$: 282.0891. The enantiomeric excess was determined on a Diacel Chiralpak AS-H stationary chiral phase at 220 nm (hexane—propan-2-ol (90 : 10), 0.5 mL min^{-1}; $t_{(R)}$ = 20.70 min (minor), 23.00 min (major)).

(*S*)-2-[(*R*)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone (5f). The yield was 12.2 mg (79%), a pale yellow powder. M.p. 80—82 °C, $[\alpha]_D^{20}$ −43.2 (*c* 0.1, $CHCl_3$), 85% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.26—1.35 (m, 1 H); 1.51—1.76 (m, 4 H); 2.01—2.04 (m, 1 H); 2.27—2.47 (m, 2 H); 2.83 (br.s, 1 H); 4.24 (br.s, 1 H); 4.82 (s, 2 H); 7.05 (t, 1 H, J = 7.6 Hz); 7.14 (d, 1 H, J = 7.6 Hz); 7.22—7.24 (m, 1 H); 7.50 (d, 1 H, J = 8.0 Hz). Found: *m/z* 326.0388 $[M + H]^+$. Calculated for $C_{14}H_{17}BrNO_3$: 326.0386. The enantiomeric excess was determined on a Diacel Chiralpak AS-H stationary chiral phase at 220 nm (hexane—propan-2-ol (90 : 10), 1.0 mL min^{-1}; $t_{(R)}$ = 16.65 min (minor), 22.48 min (major)).

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone (5g). The yield was 9.1 mg (66%), a white powder. M.p. 78—80 °C, $[\alpha]_D^{20}$ −21.3 (*c* 0.1, $CHCl_3$), 82% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.15—1.32 (m, 1 H); 1.43—1.83 (m, 4 H); 1.97—2.17 (m, 1 H); 2.25—2.47 (m, 2 H); 2.54—2.72 (m, 1 H); 3.62—3.79 (m, 4 H); 4.56 (dd, 1 H, J_1 = 12.3 Hz, J_2 = 10.1 Hz); 4.90 (dd, 1 H, J_1 = 12.3 Hz, J_2 = 4.6 Hz); 6.83 (d, 2 H, J = 8.8 Hz); 7.06 (d, 2 H, J = 8.6 Hz). Found: *m/z* 278.1389 $[M + H]^+$. Calculated for $C_{15}H_{20}NO_4$: 278.1387. The enantiomeric excess was determined on a Diacel Chiralpak AD-H stationary chiral phase at 220 nm (hexane—propan-2-ol (95 : 5), 1.0 mL min^{-1}; $t_{(R)}$ = 24.68 min (minor), 31.42 min (major)).

(*S*)-2-[(*R*)-2-Nitro-1-(4-nitrophenyl)ethyl]cyclohexanone (5h). The yield was 10.2 mg (70%), a pale yellow oil. M.p. 80—82 °C, $[\alpha]_D^{20}$ −30.3 (*c* 1.0, $CHCl_3$), 93% *ee*. ^{1}H NMR ($CDCl_3$), δ: 1.28—1.37 (m, 1 H); 1.43—1.88 (m, 4 H; 2.09—2.18 (m, 1 H); 2.25—2.52 (m, 2 H); 2.58—2.80 (m, 1 H); 3.91 (td, 1 H, J_1 = 9.8 Hz, J_2 = 4.5 Hz); 4.67 (dd, 1 H, J_1 = 13.0 Hz, J_2 = 10.2 Hz); 4.98 (dd, 1 H, J_1 = 13.0 Hz, J_2 = 4.5 Hz); 7.38 (d, 2 H, J = 8.8 Hz); 8.18 (d, 2 H, J = 8.8 Hz). Found: *m/z* 293.1136 $[M + H]^+$. Calculated for $C_{14}H_{17}N_2O_5$: 293.1132. The enantiomeric excess was determined on a Diacel Chiralpak AD-H stationary chiral phase at 220 nm (hexane—propan-2-ol (80 : 20), 0.5 mL min^{-1}; $t_{(R)}$ = 39.66 min (minor), 69.34 min (major)).

Regeneration of organocatalyst I (general procedure). After the reaction was completed, trifluoroacetic acid (22.0 μL, 0.3 mmol) was added to the reaction mixture, the solution was stirred for 30 min and concentrated. Product **5a** and unreacted starting compounds were extracted with diethyl ether (5×4 mL). The organic layer was decanted, Et_3N (43.0 μL, 0.31 mmol) was added to the remaining catalyst, the resulting mixture was washed with water (5×2 mL) and vacuum dried (1.0 Torr, 70 °C, 1 h). New portions of the starting compounds **3a** (74.5 mg, 0.5 mmol) and **4a** (103.0 μL, 1.0 mmol) were added to the regenerated catalyst **I** and the process was repeated.

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The authors declare no competing interest.

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