Asymmetric Michael reaction between aldehydes and nitroalkanes promoted by pyrrolidine-containing C_2-symmetric organocatalysts

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Bifunctional C_2-symmetric organocatalysts derived from chiral 1,2-diaminoethanes and (*S*)-2-aminomethylpyrrolidine were first used for promoting the asymmetric Michael addition of aliphatic aldehydes to nitroalkenes. The synthesized enantioenriched (up to 82% *ee*) products can be transformed into various biologically active γ-aminobutyric acid derivatives.

Key words: asymmetric catalysis, organocatalysis, squaramides, Michael reaction, aldehydes, nitroalkanes.

Asymmetric Michael addition of aldehydes and ketones to nitroalkenes promoted by chiral organocatalysts is an efficient enantioselective approach for carbon—carbon bond formation.[1,2] For instance, this reaction is widely used for synthesizing the prodrugs of pregabalin, phenibut, baclofen,[3] nakinadine B,[4] and γ-aminobutyric acid (GABA) derivatives and their analogs. The common organocatalysts for these reactions are poorly available C_1-symmetric pyrrolidine derivatives bearing either thiourea[5] or squaramide[6] moieties. These moieties provide additional activation and necessary spatial orientation of the starting reactants in the activated complex.[7] Besides, the use of high catalyst loading (up to 20 mol.%) and high-boiling aprotic solvents (DMSO, DMF) and ionic liquids is necessary to achieve high product yields and enantioselectivity.[8] All these requirements hamper the product separation and regeneration of valuable catalysts. Earlier,[9] we have shown that C_2-symmetric organocatalysts bearing squaramide moieties lack the above-mentioned drawbacks. The majority of C_2-symmetric organocatalysts are poorly soluble in organic solvents that simplifies their isolation from the reaction mixtures. To date, C_2-symmetric pyrrolidine-derived squaramides were applied only for catalyzing the reactions between ketones (mainly, cyclic ones) and nitroalkenes.[10] To the best of our knowledge, no organocatalysts of this type have been used in asymmetric Michael reactions involving aliphatic aldehydes. In the present work, we describe addition of alkanals to nitroalkenes promoted by C_2-symmetric organocatalysts.

Results and Discussion

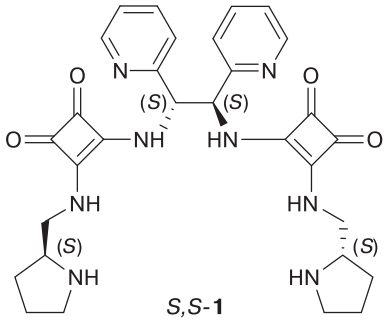
Earlier, we have synthesized new C_2-symmetric *N,N′*-bis-[(pyrrolidin-2-ylmethyl)squaramides] **1**—**3** from chiral (*R,R*)- and (*S,S*)-1,2-diaminoethanes and revealed that these compounds efficiently catalyze the addition of ketones to different nitro olefins.[10] In the present work, we widened the scope of the substrates suitable for the reactions promoted by catalysts **1**—**3** and performed the more complex asymmetric addition reactions between aliphatic aldehydes and nitro olefins.

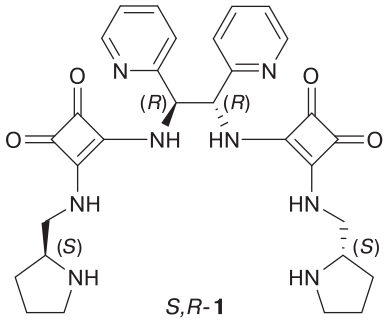
The optimal organocatalyst was identified using the model reaction of isobutyric aldehyde **4a** (2 equiv.) with β-nitrostyrene **5a** (1 equiv.). The reaction was carried out in the presence of catalysts **1**—**3** (10 mol.%) in a THF solution at room temperature (Table 1, entries *1*—*6*).

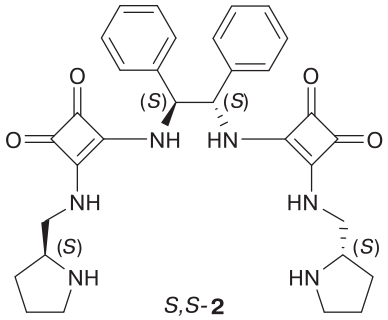
It was found that under the model reaction conditions squaramide *S,S*-**3** bearing (1*S,*2*S*)-diaminocyclohexane and (*S*)-(pyrrolidin-2-yl)methylamine moieties exhibited the highest catalytic performance. Next, we studied the effect of different solvents on the reaction between **4a** and **5a** promoted by organocatalyst *S,S*-**3**. The highest stereoinduction (76% *ee*) was achieved in toluene (see Table 1, entry *7*). Other solvents (EtOAc, CH_2Cl_2, EtOH) gave unsatisfactory results (entries *8*—*10*). To our surprise, the reaction occurs even in water to produce the target product in very high yield (86%) but with poor enantioselectivity (23% *ee*) (entry *11*).

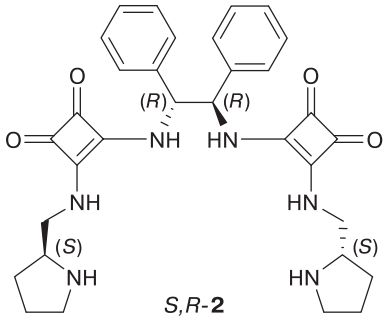
Catalyst *S,S*-**3** (10 mol.%, in toluene) providing the highest yield and enantioselectivity in the model reaction

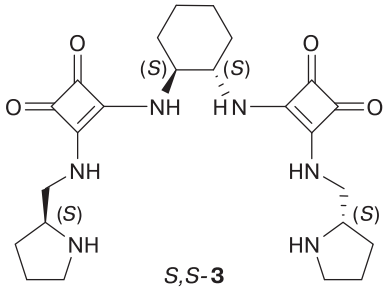
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1402—1406, July, 2019.

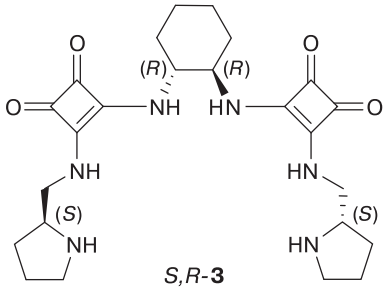




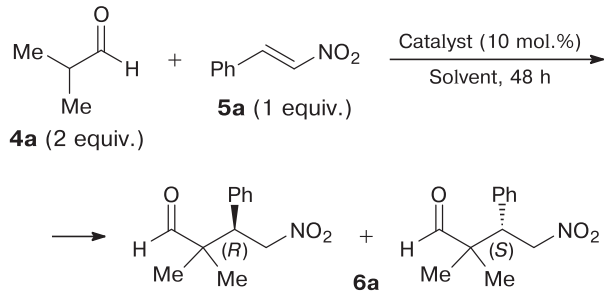








Scheme 1



was used for evaluation of the substrate scope (Scheme 2). Thus, isobutyric aldehyde **4a** efficiently reacts with aromatic nitro olefins **5**, including ones bearing the electron-donating (**5b—f**) and electron-withdrawing (**5g**) substituents at the aromatic ring, to give the target products in 66—79% yields and 70—77% *ee*. Furyl-substituted nitroalkene **5h** also reacts readily with **4a** to give product **6h** in 74% yield and 79% *ee*. It is interesting to note that nitro diene **5i** reacts with isobutyric aldehyde **4a** regiospecifically at the position 2 to afford product **6i** with moderate enantioselectivity (68% *ee*). The reaction of acetaldehyde **4b** (5 *M* solution in THF) and nitrostyrene **5a** leads to product **6j** in high yield (99%) and enantioselectivity (82% *ee*). In the case of propanal **4c**, the reaction proceeds with very high diastereoselectivity (*dr* (2*S*,3*R*) : (2*R*,3*R*) = = 95 : 5) and 63% *ee* of the major diastereomer 2*S*,3*R*-**6k** (^{1}H NMR and HPLC data).

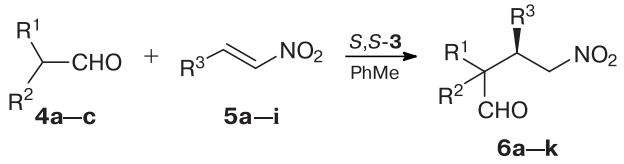
Organocatalyst *S*,*S*-**3** can be easily recovered and reused (Table 2). After the reaction completion, the reaction mixture was concentrated *in vacuo*, the products were extracted with diethyl ether, and the organic layer was decanted. Then the new portions of the starting compounds and the solvent were added to the residue and the reaction was repeated under the same conditions. After five runs, high resolution mass spectrometry reveals no changes in the structure of catalyst *S*,*S*-**3**. Some reduction of catalytic activity in the fifth run can be reasonably

Table 1. Selection of the catalyst and optimization of the reaction conditions for the synthesis of compound **6a** by the reaction of isobutyric aldehyde **4a** with β-nitrostyrene **5a**[a]

Entry	Catalyst	Solvent	Yield[b] of **6a** (%)	*ee*[c] of **6a** (%)
1	*S*,*R*-**1**	THF	16	44
2	*S*,*S*-**1**	THF	25	65
3	*S*,*S*-**2**	THF	55	50
4	*S*,*R*-**2**	THF	16	60
5	*S*,*S*-**3**	THF	56	74
6	*S*,*R*-**3**	THF	52	66
7	*S*,*S*-**3**	PhMe	70	76
8	*S*,*S*-**3**	EtOAc	53	71
9	*S*,*S*-**3**	CH_2Cl_2	45	66
10	*S*,*S*-**3**	EtOH	77	71
11	*S*,*S*-**3**	H_2O	86	23

[a] Suspension of the catalyst **1**—**3** (0.005 mmol, 10 mol.%), aldehyde **4a** (7.2 mg, 0.1 mmol), β-nitrostyrene **5a** (7.5 mg, 0.05 mmol), and the solvent (0.1 mL), ~20 °C, 48 h.
[b] Isolated yield of **6a** (silica gel flash chromatography).
[c] Enantiomeric excess was determined by HPLC on chiral phase Chiralpak AD-H; an absolute (*R*)-configuration of compound **6a** was confirmed by a comparison of its rotating angle with published data.[11]

Scheme 2



4: $R^1 = R^2$ = Me (**a**), $R^1 = R^2$ = H (**b**), R^1 = Me, R^2 = H (**c**)
5: R^3 = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 2-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-FC_6H_4 (**f**), 4-$O_2NC_6H_4$ (**g**), 2-furyl (**h**), PhCH=CH (**i**)

Compound **6**	R^1	R^2	R^3	Yield (%)	*ee* (%)
a	Me	Me	Ph	70	76
b	Me	Me	4-$MeOC_6H_4$	73	77
c	Me	Me	2-$MeOC_6H_4$	75	70
d	Me	Me	4-ClC_6H_4	79	75
e	Me	Me	4-BrC_6H_4	66	72
f	Me	Me	4-FC_6H_4	70	73
g	Me	Me	4-$O_2NC_6H_4$	81	80
h	Me	Me	2-furyl	74	79
i	Me	Me	PhCH=CH	55	68
j	H	H	Ph	99	82
k	Me	H	Ph	99*	63 (2*S*,3*R*) 22 (2*R*,3*R*)

* Diastereomeric ratio (2*S*,3*R*) : (2*R*,3*R*) = 95 : 5.

explained by the inevitable losses of the catalyst during recovery.

In summary, in the present work we pioneered in the use of a series of C_2-symmetric squaramide organocatalysts **1**—**3** in the Michael reaction of aliphatic aldehydes with nitroalkenes. We succeeded to achieve high yields (up to 99%) and enantiomeric excesses (up to 82% *ee*) of the products. It was found that nitroalka-1,3-diene **5i** reacts with isobutyric aldehyde **4a** regiospecifically at the position 2. Catalyst *S*,*S*-**3** can be recovered and reused almost without loss of catalytic activity and selectivity. A series of synthesized products **6a**—**e** seem to be valuable chiral precursors of the GABA analogs (phenibut, baclofen, rolipram, and pregabalin) and some other biologically active compounds.[12]

Table 2. Recovery of the catalyst *S*,*S*-**3** used to catalyzed the reaction between compounds **4a** and **5a**[a]

Cycle	Yield of **6a** (%)	*ee* of **6a** (%)
1	70	76
2	68	76
3	66	74
4	63	72
5[b]	60	70

[a] Reaction conditions: catalyst *S*,*S*-**3** (5 mg, 0.005 mmol, 10 mol.%), aldehyde **4a** (7.2 mg, 0.1 mmol), β-nitrostyrene **5a** (7.5 mg, 0.05 mmol), toluene (0.1 mL), ~20 °C, stirring, 48 h.
[b] Reaction time was 56 h.

Experimental

Commercially available reagents were purchased from Sigma-Aldrich Co. The solvents were purified following the standard procedures. Catalysts **1**—**3** and the starting nitro olefins **5** were synthesized as described earlier.[10,13] Column chromatography was performed with Aldrich silica gel (0.060—0.200 μm) with gradient elution with hexane—ethyl acetate (2 : 1→1 : 1). ^{1}H and ^{13}C NMR spectra were run with a Bruker AM300 instrument (working frequencies of 300 (^{1}H) and 75 MHz (^{13}C)) at 25 °C. High resolution mass spectrometry was performed with a Bruker microTOF II instrument. Enantiomeric compositions of products **6** were analyzed using a Staier HPLC system (Akvilon, Russia) equipped with a UV detector (220—254 nm) and 25-cm chiral columns Chiralpak AD-H, AS-H, and OD-H (Chiral Technologies). The racemic samples of compounds **6** used as the standards in determining the enantiomeric excesses (*ee*) by HPLC were synthesized from the corresponding reactants in the presence of pyrrolidine (10—20 mol.% in toluene).

Catalytic Michael reaction between compounds 4 and 5 (general procedure). To a suspension of organocatalyst **1**—**3** (5.0 mg, 0.005 mmol, 10 mol.%) and nitro olefin **5** (0.05 mmol) in toluene (0.1 mL), aldehyde **4a**—**c** (0.1 mmol) was added. Acetaldehyde **4b** was used as a THF solution (0.1 mmol of **4b** correspond to 20 μL of 5 *M* solution). The reaction mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. Products **6** were extracted with diethyl ether (3×4 mL) and then purified by silica gel flash chromatography (gradient elution with hexane—ethyl acetate, 2 : 1→1 : 1). Spectral properties of compounds **6** coincide with those reported earlier.[12]

(*R*)-2,2-Dimethyl-4-nitro-3-phenylbutanal (6a). Yield 6.08 mg (70%), yellow oil. $[\alpha]_D^{20}$ + 6.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 0.86 (s, 3 H, CH_3); 0.99 (s, 3 H, CH_3); 3.67—3.71 (m, 1 H, CH), 4.59 (m, 1 H, CH_2), 4.73—4.79 (m, 1 H, CH_2); 7.09—7.21 (m, 5 H, ArH); 9.39 (s, 1 H, CHO). ^{13}C NMR ($CDCl_3$), δ: 18.5, 21.2, 48.2, 48.1, 76.3, 127.6, 128.5, 128.9, 135.3, 204.2. Found: *m/z* 222.1128 $[M + H]^+$. $C_{12}H_{16}NO_3$. Calculated: M = 222.1125. Enantiomeric excess was determined using HPLC on a stationary chiral phase Chiralpak AD-H, detection at 220 nm (hexane—propan-2-ol (98 : 2), 0.5 mL min^{-1}; $t_{(R)}$ = 24.7 min, $t_{(S)}$ = 25.8 min).

(*R*)-3-(4-Methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (6b). Yield 7.66 mg (73%), yellow oil. $[\alpha]_D^{20}$ −5.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.01 (s, 3 H, CH_3); 1.13 (s, 3 H, CH_3); 3.74 (dd, 1 H, CH, *J* = 11.4 Hz, *J* = 4.5 Hz); 3.79 (s, 3 H, OCH_3); 4.66 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 4.2 Hz); 4.81 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 11.4 Hz); 6.84 (d, 2 H, Ar, *J* = 8.7 Hz); 7.11 (d, 2 H, Ar, *J* = 8.7 Hz); 9.51 (s, 1 H, CHO). Found: *m/z* 252.1228 $[M + H]^+$. $C_{13}H_{18}NO_4$. Calculated: M = 252.1231. Enantiomeric excess was determined using HPLC on a stationary chiral phase Chiralpak OD-H, detection at 220 nm (hexane—propan-2-ol (75 : 25), 0.8 mL min^{-1}; $t_{(R)}$ = 15.2 min, $t_{(S)}$ = 21.3 min).

(*R*)-3-(2-Methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (6c). Yield 7.38 mg (75%), yellow oil. $[\alpha]_D^{20}$ +14.4 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.05 (s, 3 H, CH_3); 1.1 (s, 3 H, CH_3); 3.82 (dd, 1 H, CH, *J* = 11.1 Hz, *J* = 3.6 Hz); 4.57 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 3.6 Hz); 4.75 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 11.1 Hz); 6.21 (d, 1 H, Ar, *J* = 3.0 Hz); 6.95 (s, 1 H, Ar); 7.12 (s, 1 H, Ar); 9.51 (s, 1 H, CHO). Found: *m/z* 251.2784 $[M + H]^+$. $C_{13}H_{17}NO_4$. Enantiomeric excess was determined using HPLC on a stationary chiral phase Chiralpak OD-H, detection at 254 nm (hexane—propan-2-ol (80 : 20), 0.7 mL min^{-1}; $t_{(R)}$ =12.7 min, $t_{(S)}$ = 21.3 min).

(*R*)-3-(4-Chlorophenyl)-2,2-dimethyl-4-nitrobutanal (6d). Yield 9.05 mg (79%), yellow oil. $[\alpha]_D^{20}$ +3.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.01 (s, 3 H, CH_3); 1.13 (s, 3 H, CH_3); 3.77 (dd, 1 H, CH, *J* = 11.4 Hz, *J* = 4.2 Hz); 4.68 (dd, 1 H, CH_2, *J* = 13.2 Hz, *J* = 4.2 Hz); 4.82 (dd, 1 H, CH_2, *J* = 13.2 Hz, *J* = 11.4 Hz); 7.12 (t, 1 H, Ar, *J* = 2.4 Hz); 7.15 (t, 1 H, Ar, *J* = 2.4 Hz); 7.29 (t, 1 H, Ar, *J* = 2.4 Hz); 7.32 (t, 1 H, Ar, *J* = 2.4 Hz); 9.48 (s, 1 H, CHO). Found: *m/z* 256.0732 $[M + H]^+$. $C_{12}H_{15}ClNO_3$. Enantiomeric excess was determined using HPLC on a stationary chiral phase Chiralpak OD-H, detection at 220 nm (hexane—propan-2-ol (75 : 25), 0.8 mL min^{-1}; $t_{(R)}$ = 13.7 min, $t_{(S)}$ = 20.1 min).

(*R*)-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal (6e). Yield 7.92 mg (66%), yellow oil. $[\alpha]_D^{20}$ +2.0 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.00 (s, 3 H, CH_3); 1.12 (s, 3 H, CH_3); 3.77 (dd, 1 H, CH, *J* = 4.0 Hz, *J* = 11.2 Hz); 4.68 (dd, 1 H, CH_2, *J* = 4.0 Hz, *J* = 13.2 Hz); 4.83 (dd, 1 H, CH_2, *J* = 11.2 Hz, *J* = 13.2 Hz); 7.10 (d, 2 H, Ar, *J* = 8.4 Hz); 7.47 (d, 2 H, Ar, *J* = 8.4 Hz); 9.49 (s, 1 H, CHO). Found: *m/z* 300.0225 $[M + H]^+$. $C_{12}H_{15}BrNO_3$. Calculated: M = 300.0230. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 254 nm (hexane—propan-2-ol (80 : 20), 0.7 mL min^{-1}; $t_{(R)}$ = 22.0 min, $t_{(S)}$ = 34.5 min).

(*R*)-(4-Fluorophenyl)-2,2-dimethyl-4-nitrobutanal (6f). Yield 7.65 mg (70%), yellow oil. $[\alpha]_D^{20}$ +1.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.01 (s, 3 H, CH_3); 1.13 (s, 3 H, CH_3); 3.77—3.81 (m, 1 H, CH); 4.67—4.72 (m, 1 H, CH_2); 4.80—4.86 (m, 1 H, CH_2); 7.01—7.05 (m, 2 H, Ar); 7.17—7.21 (m, 2 H, Ar); 9.51 (s, 1 H, CHO). Found: *m/z* 240.1033 $[M + H]^+$. $C_{12}H_{15}FNO_3$. Calculated: M = 240.1031. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 254 nm (hexane—propan-2-ol (80 : 20), 0.7 mL min^{-1}; $t_{(R)}$ = 16.2 min, $t_{(S)}$ = 30.5 min).

(*R*)-2,2-Dimethyl-4-nitro-3-(4-nitrophenyl)butanal (6g). Yield 9.31 mg (81%), yellow oil. $[\alpha]_D^{20}$ +8.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.06 (s, 3 H, CH_3); 1.17 (s, 3 H, CH_3); 3.94 (dd, 1 H, CH, *J* = 13.5 Hz, *J* = 3.9 Hz); 4.77 (dd, 1 H, CH_2, *J* = 13.5 Hz, *J* = 3.9 Hz); 4.90 (t, 1 H, CH_2, *J* = 13.5 Hz); 7.42 (d, 2 H, Ar, *J* = 8.7 Hz); 8.21 (d, 2 H, Ar, *J* = 8.7 Hz); 9.48 (s, 1 H, CHO). Found: *m/z* 267.0973 $[M + H]^+$. $C_{12}H_{15}O_5N_2$. Calculated: M = 267.0975. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 220 nm (hexane—propan-2-ol (75 : 25), 0.8 mL min^{-1}; $t_{(R)}$ = 25.5 min, $t_{(S)}$ = 39.6 min).

(*R*)-3-(2-Furyl)-2,2-dimethyl-4-nitrobutanal (6h). Yield 6.33 mg (74%), yellow oil. $[\alpha]_D^{20}$ −19.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.05 (s, 3 H, CH_3); 1.18 (s, 3 H, CH_3); 3.92 (dd, 1 H, CH, *J* = 11.1 Hz, *J* = 3.6 Hz); 4.57 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 3.6 Hz); 4.75 (dd, 1 H, CH_2, *J* = 12.6 Hz, *J* = 11.1 Hz); 6.21 (d, 1 H, Ar, *J* = 3.0 Hz); 6.30 (s, 1 H, Ar); 7.36 (s, 1 H, Ar); 9.50 (s, 1 H, CHO). Found: *m/z* 212.0920 $[M + H]^+$. $C_{10}H_{13}O_4N$. Calculated: M = 212.0918. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 220 nm (hexane—propan-2-ol (75 : 25), 0.8 mL min^{-1}; $t_{(R)}$ = 9.5 min, $t_{(S)}$ = 14.0 min).

(*R*)-2,2-Dimethyl-3-nitromethyl-5-phenylpent-4-enal (6i). Yield 5.28 mg (55%), yellow oil. $[\alpha]_D^{20}$ −1.9 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 1.17 (s, 3 H, CH_3); 1.18 (s, 3 H); 3.30 (m, 1 H); 4.51 (m, 2 H), 6.03 (dd, 1 H, *J* = 15.7 Hz, *J* = 9.8 Hz); 6.54 (d, 1 H, *J* = 15.7 Hz); 7.25—7.37 (m, 5 H, Ar); 9.53 (s, 1 H, CHO). Found: *m/z* 265.1546 $[M + NH_4]^+$. $C_{14}H_{21}N_2O_3$. Calculated: M = 265.1552. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 220 nm (hexane—propan-2-ol (80 : 20), 0.8 mL min^{-1}; $t_{(R)}$ = 15.1 min, $t_{(S)}$ = 16.4 min).

(*R*)-4-Nitro-3-phenylbutanal (6j). Yield 9.65 mg (99%), yellow oil. $[\alpha]_D^{20}$ −7.1 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 2.95 (d, 2 H, CH_2, *J* = 7.1 Hz); 4.03—4.16 (m, 1 H, CH); 4.58—4.72 (m, 2 H, CH_2); 7.20—7.40 (m, 5 H, Ar); 9.71 (t, 1 H, CHO, *J* = 1.9 Hz). Found: *m/z* 194.0815 $[M + H]^+$. $C_{10}H_{12}NO_3$. Calculated: M = 194.0812. Enantiomeric excess was determined by HPLC on a stationary chiral phase Chiralpak AS-H using detection at 220 nm (hexane—propan-2-ol (70 : 30), 1.0 mL min^{-1}; $t_{(R)}$ = 14.5 min, $t_{(S)}$ = 19.2 min).

(3*R*)-2-Methyl-4-nitro-3-phenylbutanal (6k). Yield 10.25 mg (99%), yellow oil. $[\alpha]_D^{20}$ +8.3 (*c* 1.0, $CHCl_3$). ^1H NMR of a diastereomeric mixture ($CDCl_3$), δ: 0.89 (d, 3 H, CH_3, *J* = 7.3 Hz); 2.66—2.72 (m, 1 H, CH); 3.70—3.76 (m, 1 H, CH); 4.57—4.62 (m, 1 H, CH_2); 4.69—4.74 (m, 1 H, CH_2); 7.07—7.27 (m, 5 H, Ar); 9.54 (s, 0.05 H, CHO, (2*R*,3*R*)-isomer); 9.71 (s, 0.95 H, CHO, (2*S*,3*R*)-isomer). Found: *m/z* 208.0972 $[M + H]^+$. $C_{11}H_{14}NO_3$. Calculated: M = 208.0969. Isomeric composition was determined by HPLC on a stationary chiral phase Chiralpak OD-H using detection at 220 nm (hexane—propan-2-ol (80 : 20), 0.8 mL min^{-1}; $t_{(2S,3R)}$ = 25.3 min, $t_{(2S,3S)}$ = 19.2 min; $t_{(2R,3R)}$ = = 28.6 min, $t_{(2S,3R)}$ = 22.8 min).

Recovery of organocatalyst *S*,*S*-3 (general procedure). After completion of the reaction, the mixture was concentrated

in vacuo. Product **6a** and unreacted starting compounds were extracted with diethyl ether and the organic layer was decanted. The remaining catalyst *S*,*S*-**3** was dried *in vacuo* (1.0 Torr, 50 °C, 1 h) and then a new portions of the starting compounds **4a** (7.2 mg, 0.1 mmol) and **5a** (7.5 mg, 0.05 mmol) and toluene (0.1 mL) were added. The reactions were carried out as described above.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 18-33-00930).

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Received March 21, 2019;
in revised form April 16, 2019;
accepted April 26, 2019