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Towards sustainable amino acid-derived organocatalysts for asymmetric *syn*-aldol reactions

Vasiliy V. Gerasimchuk, Alexandr S. Kucherenko, Artem N. Fakhrutdinov, Michael G. Medvedev, Yulia V. Nelyubina, and Sergei G. Zlotin*

Abstract: Undesirable side processes responsible for fast deactivation of primary amino acid-derived organocatalysts in asymmetric aldol reactions have been identified. Novel ionic liquid-supported (*S*)-valine / (*S*)-α,α-diphenylserinol-derived catalyst **9** designed basing on these results exhibited much better recyclability in asymmetric *syn*-aldol reaction between hydroxyacetone and aldehydes. Furthermore, this catalyst appeared useful for the stereoselective synthesis of the naturally occurring 1(*3H*)-isobenzofuran-1-one scaffold *via* the asymmetric *syn*-aldol / lactonization cascade reaction.

Introduction

The asymmetric aldol reaction that occurs in Nature stands among the most important C-C bond forming interactions and is highly applicable to the enantioselective synthesis of bioactive molecules.[1] An efficient catalytic version of this reaction is based on the use of amino acid-derived chiral organocatalysts, which may act differently depending on their structure.[2] As a rule, major products of secondary amine-catalyzed aldol reactions have the *anti*-configuration.[3] However, in the presence of organocatalysts bearing primary amino groups[4] or their prototypes – native enzymes (aldolases),[5] *syn*-aldols, which are key structural fragments of carbohydrates, are formed. In a series of primary amine organocatalysts, amino acids **1**[4a,b,6] or **2**,[7] their amides **3**,[8] **4**[9] or **5**[10] and some other aminocatalysts[11] exhibit promising catalytic performance (Figure 1 a).

In contrast to high-molecular enzymes, small-sized catalysts **1**-**5** are not recyclable.[4,6-10] To our knowledge, just two supported primary amino acid-derived catalysts **6**[12] and **7**[13] for the *syn*-aldol reaction have been so far reported (Figure 1 b). However, ionic liquid-supported catalyst **7** could not operate for more than 2–3 cycles (afterwards, a significant conversion and/or reaction rate decrease was observed)[13] and no recycling experiment with polystyrene-tagged threonine **6** in the corresponding *syn*-aldol reaction was run. It should be noted that supported secondary amines (including proline derivatives)[14a,b] and some H-bonding organocatalysts[14c-e] exhibit much higher sustainability in catalytic reactions.

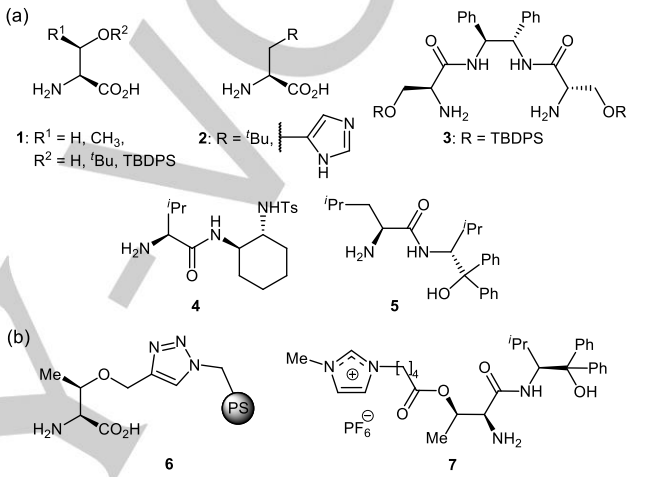

Figure 1. Unsupported (a) and supported (b) primary amino acid-derived organocatalysts for asymmetric *syn*-aldol reactions.

Results and Discussion

In order to identify a reason for deactivation of catalyst **7** and, basing on this information, to find a way to more sustainable primary amino acid-derived organocatalysts for asymmetric *syn*-aldol reactions we undertook a detailed two-dimensional NMR study (^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC experiments)[15] with starting and "aged" samples of the catalyst. First, using correlations in these experiments, we unequivocally assigned chemical shifts with H_2 (δ = 4.85 ppm) and H_3 (δ = 3.90 ppm) protons and C_1 (δ = 171.6 ppm) and C_4 (δ = 167.8 ppm) carbons in the freshly synthesized sample of **7** (Scheme 1). However, the ^{1}H-^{13}C HMBC spectrum of the "aged" catalyst that operated the reaction between hydroxyacetone and 4-nitrobenzaldehyde over 72 h was different. There was no correlation between C_1 and H_2 as in the previous spectra. Instead, a novel, impossible for **7**, correlation between C_1 and H_3 was observed. In addition to the expected cross-peak between C_4 and H (δ = 7.47 ppm, amide group proton), a correlation between C_1 and H (δ = 7.95 ppm, another proton of the amide group), was identified. Moreover, along with the absence of the primary amino group signal there were two protons of hydroxyl groups (according to ^{1}H-^{13}C HSQC data), while only one was present in catalyst **7**. These data strongly evidence to the complete transformation of initial catalyst **7** to isomeric compound **8** due to the *O-N* migration of the carbonyl group (see Scheme 1).

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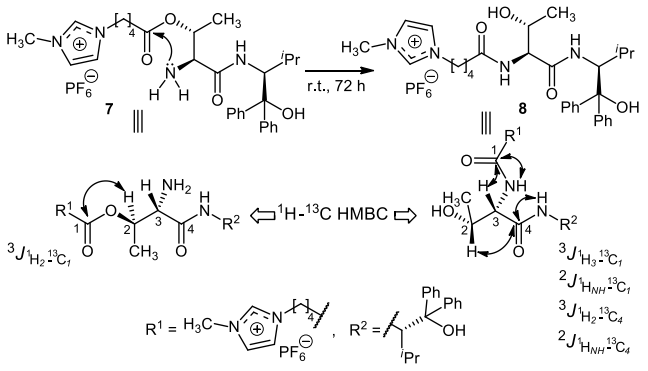
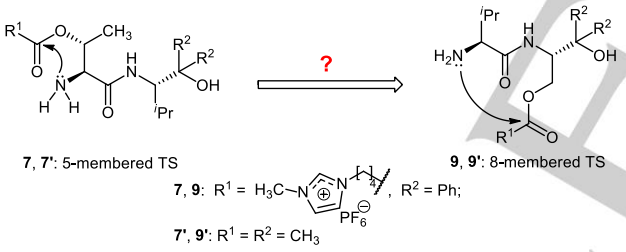


Scheme 1. Transformation of **7** to **8** according to ^{1}H-^{13}C HMBC and HSQC data (for copies of the ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC experiments see Supporting info).

The *O*-*N*-migration of the acyl or alkoxycarbonyl group in primary amino acid derivatives[16a,b] has never been considered as a side reaction responsible for deactivation of primary amine-derived organocatalysts.[16c] The rearrangement was shown to proceed *via* the five-membered cyclic transition state (TS) (the entropy factor),[17] which was readily achievable in the case of compound **7**.[18] Therefore, we supposed that a simple displacement of the acyl spacer group from the threonine unit of catalyst **7** to the distal amidoalcohol fragment of corresponding dipeptide-like molecule **9** might significantly slow down the parasitic *O*-*N*-migration rate (Scheme 2).



Scheme 2. Research strategy.

With this hypothesis in view, we first performed a quantum chemical study for all possible conformations of model compounds **7'** and **9'** (simpler analogs of corresponding catalysts **7** and **9**). The calculated distances between primary amine nitrogen *4* and ester carbonyl carbon *5* in the minimum-energy conformations were different for **7'** (4.16 Å) and **9'** (5.6 Å) (Figure 2). However, these compounds had remarkably similar steric environments of the primary amino group which promised their similar performance in the enamine catalysis. Next, the geometry of compound **9** was reconstructed basing on the located **9'** minimum geometry and optimized at the PBE0-D3/cc-pVTZ level of theory with SMD-modeled toluene solvation effects. The QTAIM[19] analysis and subsequent application of the EML[20] correlation for the noncovalent interaction strength revealed strong hydrogen bonds between proton *1* and oxygen *2* (~12.8 kcal·mol^{-1}) as well as between amine nitrogen *4* and proton *3* (~6.9 kcal·mol^{-1}), which should additionally stabilize the open-chained conformation of **9** and prevent the intramolecular approach of the amine unit to the ester group required for the undesirable *O*-*N*-migration.

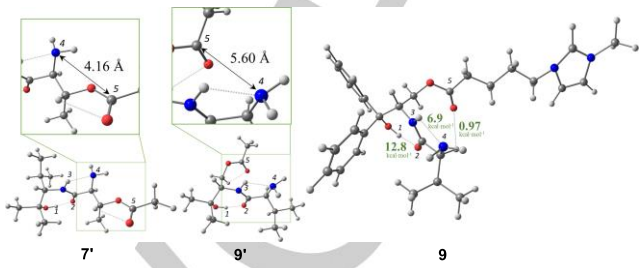
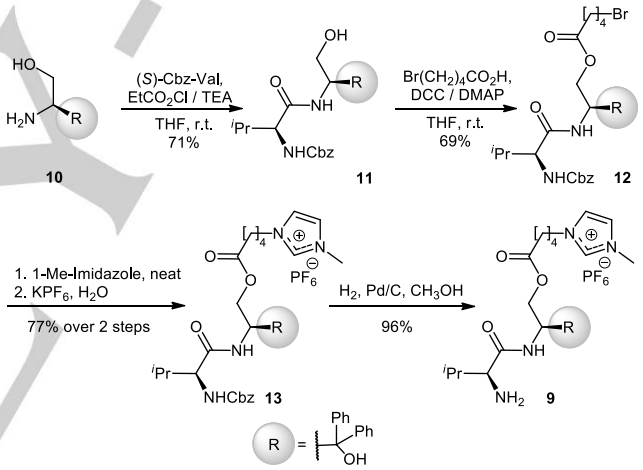


Figure 2. Minimum-energy conformers of model compounds **7'**, **9'** and supported catalyst **9** optimized at the RIJCOSX-PBE0-D3-gCP/def2-TZVP SMD and PBE0-D3/cc-pVTZ SMD (toluene) level of theory (for Cartesian coordinates see Supporting info).

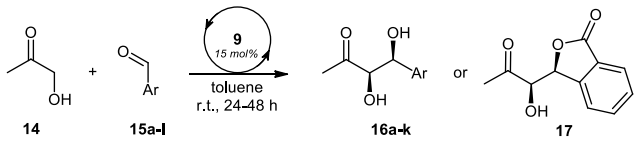


Scheme 3. Synthesis of catalyst **9**.

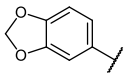
With this results in hand, we synthesized novel ionic liquid supported amino amide **9** containing (*S*)-valine and (*S*)-α,α-diphenylserinol fragments according to Scheme 3.

Catalytic performance of compound **9** was examined in asymmetric reactions of hydroxyacetone **14** with benzaldehyde derivatives **15** under conditions optimal for original catalyst **7**[13] (15 mol% of **9**, toluene, r.t.). As expected, corresponding *syn*-aldols **16** were generated in high yields with high to excellent diastereo- (*syn*/*anti* up to 96:4) and enantioselectivity (up to 99% *ee*) (Table 1). Compounds **15j** and **15k,** bearing two electron-donating methoxy groups or the dioxolane ring, appeared less active substrates under the proposed conditions (48 h) and afforded *syn*-products **16j** and **16k** with somewhat lower *dr* (*syn*/*anti* 80:20 – 85:15) and *ee* values (68–71%) (entries 10 and 11). The synthetic procedure is scalable (at least fivefold, see entry 1).

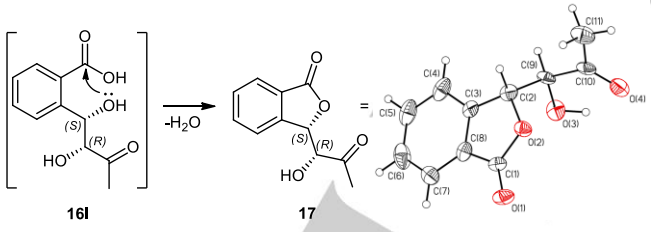
Table 1. 9-Catalyzed asymmetric *syn*-aldol reactions of hydroxyacetone **14** with aldehydes **15**.[a]



14 **15a-l** **16a-k** **17**

Entry	**15** (Ar)	**16** or **17**	Time, h	Conv. of **15**, %[b,c]	*dr* (*syn*/*anti*)[b,c]	ee (*syn*), %[b,d]
1	**15a** (2-ClC_6H_4)	**16a**	24	99, (96) [99, 97, 95, 93, 90, 84, 77][e]	96:4 (97:3) [96:4 – 96:4][e]	92 (97) [92 – 92][e]
2	**15b** (2-BrC_6H_4)	**16b**	24	90	92:8	91
3	**15c** (2-$O_2NC_6H_4$)	**16c**	24	94 (94)	95:5 (97:3)	95 (97)
4	**15d** (2-MeC_6H_4)	**16d**	36	85	80:20	91
5	**15e**(3-$O_2NC_6H_4$)	**16e**	36	98	95:5	96
6	**15f** (4-$O_2NC_6H_4$)	**16f**	24	97 (99)	93:7 (93:7)	94 (94)
7	**15g** (4-FC_6H_4)	**16g**	36	90	80:20	89
8	**15h** (4-MeC_6H_4)	**16h**	24	84, 71[f]	90:10	90
9	**15i** (4-$MeOC_6H_4$)	**16i**	24	92, 80[f] (79)	92:8 (96:4)	99 (96)
10	**15j** (3,5-$(MeO)_2C_6H_3$)	**16j**	48	95, 69[f]	85:15	71
11	**15k** 	**16k**	48	92, 74[f]	80:20	68
12	**15l** (2-$HO_2CC_6H_4$)	**17**	70	71, 40[f,g]	80:20, 99:1[g,h]	71, 98[g,h]

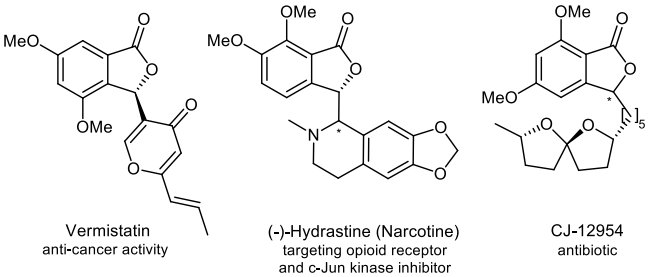
[a] Unless otherwise specified, all reactions were carried out with **14** (15 mg, 14 µL, 0.2 mmol), **15** (0.066 mmol), **9** (6.5 mg, 0.01 mmol), and toluene (90 µL). [b] Data for catalyst **7** are given in parentheses. [c] ^{1}H NMR spectroscopic data ($J^3{}_{syn}$= 0–4 Hz, $J^3{}_{anti}$= 5–8 Hz). [d] HPLC data (Daicel Chiralpak AD-H) for crude compounds **16**. [e] Subsequent data for catalyst **9** recycling (from 1st to 7th cycle) are given in square brackets. The reaction was carried out with 5-fold scaling of initial reagents. [f] Isolated yield after column chromatography of raw products. [g] Data after single recrystallization from benzene. [h] Determined by ^{1}H and ^{19}F NMR analysis of (*S*)-MTPA-derivatized compound **17** (see Supporting info).[21]



16l **17**

Scheme 4. Lactonization of **16l** and the ORTEP view of **17**.

The reaction of **14** with 2-carboxybenzaldehyde (**15l**) was accompanied by the lactonization of intermediate aldol **16l**. Corresponding product was obtained as single diastereomer with 98% *ee* by careful crystallization from benzene. The lactonization product was unambiguously assigned as (*S*)-3-((*R*)-1-hydroxy-2-oxopropyl)isobenzofuran-1(3H)-one **17** based on the ^{1}H-^{13}C 2D NMR experiments and the X-ray diffraction study (Scheme 4). To our knowledge, this reaction is the first *syn*-selective asymmetric catalytic synthesis of the 3-substituted phthalide scaffold (for corresponding *anti*-selective reactions see ref.[22]) in a large collection of natural biologically active compounds such as Vermistatin,[23a] (-)-Hydrastine,[23b] CJ-12954[23c] and others[23d,e] (Scheme 5**)**.



Vermistatin
anti-cancer activity

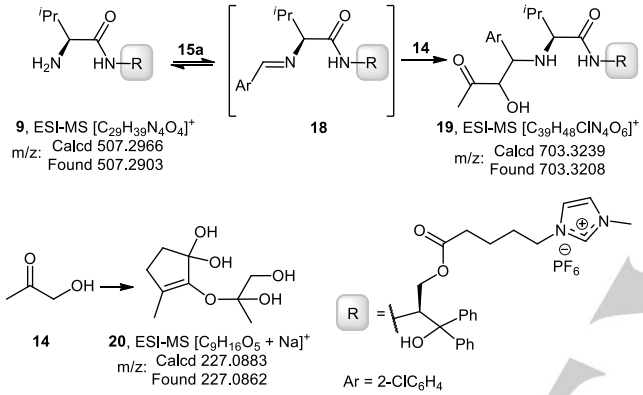
(-)-Hydrastine (Narcotine)
targeting opioid receptor
and c-Jun kinase inhibitor

CJ-12954
antibiotic

Scheme 5. Naturally occurring chiral 3-substituted phthalides with reported biological activities.

Catalyst **9** could be recycled over 7 times in the asymmetric reaction between **14** and **15a** without a negative impact on stereoinduction with only a slight catalytic activity decrease (Table 1, entry 1). The latter may be attributed to the “off-cycle”

reaction of **9** with aldehyde **15a** followed by irreversible Mannich-type addition of **14** to resulting Schiff base **18** to afford by-product **19** (Scheme 6). The known trimerization of **14** to hemiacetal **20**[24] may also contribute to slow deactivation of **9** *via* gradual adsorption of trimer **20,** poorly soluble in diethyl ether, on the catalyst surface, which reduces efficiency of the asymmetric catalysis. Intensive peaks of corresponding by-products **19** and **20** were detected in the ESI-MS spectra of the seven-fold-recycled catalyst sample along with the peak of partly deactivated catalyst **9** (for the ESI-MS methodology used in the study of deactivation pathways of ionic liquid-supported primary amine organocatalysts see ref.[25]). The by-side generation of hydroxyacetone oligomers during the catalytic reaction was also in conformity with a gradual recovered catalyst mass increase in each next cycle (total increase over 7 cycles was 17%) (see Supporting info).



Scheme 6. By-products generated in the **9**-catalyzed reaction between **14** and **15a** according to the ESI-MS spectra of seven-fold-recycled catalyst **9**.

Conclusions

In summary, undesirable side processes responsible for fast deactivation of primary amino acid derivatives in catalytic reactions were identified by means of two-dimensional NMR (^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC) and ESI-MS experiments and quantum chemistry. The intramolecular *O*-*N* migration of the acyl spacer group and (to a less extent) the Schiff-base formation and hydroxyacetone oligomerization contribute to the catalyst destruction. Novel primary amino amide **9** properly supported with the ionic group has been designed and exhibited promising sustainability in asymmetric *syn*-aldol reactions. Furthermore, the developed catalyst appeared applicable to the stereoselective synthesis of the naturally occurring 1(*3H*)-isobenzofuran-1-one scaffold *via* an asymmetric *syn*-aldol / lactonization cascade reaction.

Experimental Section

General procedure for *syn*-aldol reaction: aldehyde **15a-k** (0.066 mmol) and catalyst **9** (6.5 mg, 0.01 mmol) were dissolved in dry toluene (90 µL). Then, hydroxyacetone **14** (15 mg, 14 µL, 0.2 mmol) was added to the resulting solution. The reaction mixture was stirred at ambient temperature for 24-48 h (TLC-monitoring), filtered through a silica gel pad and evaporated (40°C, 8 mbar). Conversions and *dr* values of aldol products **16** were measured by ^{1}H NMR spectroscopy. The *ee* values of aldol products **16** were determined by chiral HPLC column (Daicel Chiralpak AD-H). NMR spectra and HPLC data for aldol products **16a**–**k** were in agreement with reported data (**16a,b**,[26a] **16c,e,f**,[26b] **16h**,[26c] **16d,g-i**[13,26d]).

(3R,4S)-4-(3,5-dimethoxyphenyl)-3,4-dihydroxybutan-2-one **(16j)**: ^{1}H NMR (500 MHz, $CDCl_3$): 2.22 (s, 3H, CH_3), 3.90 (d, 6H), 4.37 (s, 1H), 4.93 (d, *J*=2.69Hz, 2H), 6.83-7.05 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): 27.1, 56.5, 74.6, 81.4, 109.5, 110.2, 111.6, 119.3; HRMS (ESI) m/z calcd. for [$C_{12}H_{16}O_5$+Na]: 263.0890; found: 263.0898; *ee* value was determined on Chiralpak AD-H, 1 ml/min, hexane:*i*-PrOH=80:20, λ=254 nm, t_{minor}=12.0 min, t_{major}=16.7 min.

(3*R*,4*S*)-4-(benzo[d][1,3]dioxol-5-yl)-3,4-dihydroxybutan-2-one **(16k)**: ^{1}H NMR (500 MHz, $CDCl_3$): 2.19 (3H, s, CH_3), 4.30 (d, *J*=3.45Hz, 1H), 4.89 (d, *J*=3.42Hz, 1H), 5.93 (s, 2H), 6.72-6.97 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): 27.1, 74.5, 81.4, 101.7, 107.5, 107.6, 108.7, 120.4, 134.6, 148.0, 148.5, 208.8; HRMS (ESI) m/z calcd. for [$C_{11}H_{12}O_5$+Na]: 247.0577; found: 247.0582; *ee* value was determined on Chiralpak AD-H, 1 ml/min, hexane:*i*-PrOH=80:20, λ=220 nm, t_{minor}=12.6 min, t_{major}=16.1 min.

Catalyst recycling procedure: after 24 h, the mixture of hydroxyacetone (**14**) (74 mg, 70µl, 1 mmol), 2-chlorobenzaldehyde (**15a**) (46.8 mg, 0.33 mmol), catalyst **9** (32.5 mg, 0.05 mmol) and toluene (0.45 mL) was gently evaporated (40°C, 8 mbar). Product **16a** and unchanged starting compounds were carefully extracted from the residue by Et_2O (3 x 0.7mL). Fresh portions of reagents and toluene were added to the remaining catalyst **9** and catalytic procedure was re-performed as described above.

Synthesis of (*S*)-3-((*R*)-1-hydroxy-2-oxopropyl)isobenzofuran-1(3H)-one (17): 2-Carboxybenzaldehyde (**15l**) (49.5 mg, 0.33 mmol) and catalyst **9** (32 mg, 0.05 mmol) were dissolved in dry toluene (500 µL). Then, hydroxyacetone (**14**) (75 mg, 70 µL, 1.0 mmol) was added to the resulting solution. The reaction mixture was stirred at ambient temperature for 70 h (TLC-monitoring), filtered through a silica pad and purified by column chromatography (silica gel, EtOAc/*n*-hexane 1:3, $R_f \approx$ 0.20) to afford 48 mg of crude **17** (71%) as white powder, *syn/anti* 80:20. The crude product was carefully (≤60°C) dissolved in benzene (200µL) and the solution was left overnight at ambient temperature. The precipitated crystals were collected by filtration to afford 27 mg (40%) of diastereomerically pure (3*R*, 4*S)*-**17**. To determine enantiomeric purity of **17**, corresponding crude and recrystallized samples were derivatized with (*S*)-MTPA.[6] The 1 mL round-bottom flask was charged with **17** (19 mg, 0.09 mmol), DCC (47 mg, 0.23 mmol) and DMAP (3 mg, 0.025 mmol). Then, a solution of (*S*)-MTPA (38 mg, 0.16 mmol) in dry $CDCl_3$ (700 µL) was added and the mixture was stirred at 0°C for 8 h (^{1}H NMR monitoring). Then, for achieving a 100% conversion, fresh portion of DCC (20 mg, 10 mmol) was added to the reaction mixture and it was stirred for additional 2 h. According to ^{19}F NMR spectra (500MHz, $CDCl_3$) of thus obtained (*S*)-MTPA-**17** ester solution (δ_{major} -72.10 ppm, δ_{minor} -72.43 ppm, $\delta_{(S)\text{-MTPA}}$ -71.70 ppm), the *ee* values of the raw and the recrystallized samples of **17** were 71% and 98% respectively. Colorless needles, m.p. = 77-79°C, $[\alpha]_D$ = +96.1 (c 1, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d6): 2.22-2.34 (s, 3H, CH_3); 4.62-4.73 (dd, J_1=1.83 Hz, J_2=6.80 Hz, 1H, C*H*(OH)); 5.64-5.70 (d, *J*=6.80 Hz, 1H, CH); 6.0-6.09 (d, *J*=1.82 Hz, 1H, OH); 7.56-7.63 (t, *J*=7.31, 1H, CH); 7.73-7.87 (dt, J_1=7.40 Hz, J_2=12.98 Hz, 3H, CH); ^{13}C NMR (100 MHz, DMSO-d6): 27.2, 76.4, 81.7, 123.4, 125.1, 126.7, 129.7, 134.6, 148.0, 170.3, 209.4; HRMS (ESI) m/z calcd. for [$C_{11}H_{10}O_4$+Na]: 229.0471; found: 229.0479.

^{1}H Monitoring of 17 derivatization with (*S*)-MTPA: The 1 mL round-bottom flask was charged with **17** (19 mg, 0.09 mmol), DCC (47 mg, 0.23 mmol) and DMAP (3 mg, 0.025 mmol). Then, a solution of (*S*)-MTPA (38 mg,

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Keywords: organocatalysis • aldol reaction • NMR spectroscopy • quantum chemistry • ESI-MS spectrometry

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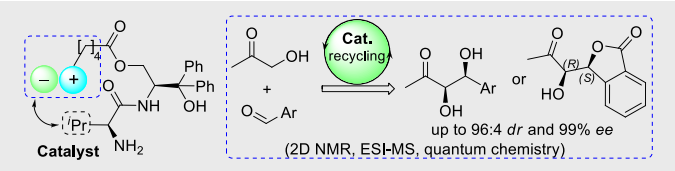

Undesirable side processes responsible for fast deactivation of primary amino acid-derived organocatalysts have been identified. Novel ionic liquid-supported (*S*)-valine / (*S*)-α,α-diphenylserinol-derived catalyst has been designed basing on these results and exhibited promising sustainability in asymmetric *syn*-aldol reactions.

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