Supplementary Material

Novel L-threonine-based ionic liquid supported organocatalyst for asymmetric syn-aldol reaction: activity and recyclability design


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General information

$^1$H and $^{13}$C NMR spectra were recorded with a Bruker AM 300 spectrometer in CDCl$_3$ and DMSO-$d_6$. The chemical shifts of $^1$H and $^{13}$C signals were measured relative to Me$_4$Si or CDCl$_3$, respectively. The high-resolution mass spectra (HRMS) were measured with a Bruker microTOF II spectrometer using electrospray ionization (ESI). The measurements were taken either in the positive ion mode (interface capillary voltage 4500 V) or in the negative ion mode (3200 V) in a mass range $m/z = 50$–3000 Da; external or internal calibration was done with electrospray calibrant solution (Fluka). Syringe injection was used for solution in MeCN/H$_2$O (1:1, v/v) (flow rate 3 μL/min). Nitrogen was applied as a dry gas, and the interface temperature was set at 180 °C. Silica gel 0.060–0.200 μm (Acros) was used for column chromatography. Threonineamide 2 and benzyl 5-(1Himidazol-1-yl)pentanoate 3 were synthesized according to known methods. Compounds 5 and 6 were purchased from Aldrich and used without purification. The solvents were purified by standard procedures. For experimental details and spectral or HPLC data see Supporting Information.

General scheme of catalyst 1c synthesis

Steps before compound 2 are described in ref [1].
Synthesis and characterization of 4

3-(5-(benzyl oxy)-5-oxopentyl)-1-(5-(((2R,3S)-3-(((benzyl ox y)carbonyl)amino)-4-oxobutan-2-yl)oxy)-5-oxopentyl)-1H-imidazol-3-ium hexafluorophosphate

Benzyl 5-(1H-imidazol-1-yl)pentanoate 4 (0.22 g, 0.83 mmol) was gradually added to a solution of (2R,3S)-3-(((benzyl ox y)carbonyl)amino)-4-oxobutan-2-yl 5-bromopentanoate 3 (0.45 g, 0.69 mmol) in CH₃OH (2 mL). The reaction mixture was kept at ambient temperature for 10 min and evaporated under reduced pressure (20 Torr) at 40 °C. The residue was heated at the same pressure (rotary evap orator, 80 °C) for 5 min, cooled to ambient temperature and diluted with distilled water (3.0 mL). A solution of KPF₆ (128 mg, 0.69 mmol) in distilled water (1.5 mL) was added to the resulting aqueous solution and the reaction mixture was stirred for 1 h at ambient temperature. The precipitate was filtered and washed successively with distilled water (3 x 3 mL) and then 2 x 1 mL of Et₂O, then dried on filter to obtain 0.612 g (90%) of white powder 3-(5-(benzyl oxy)-5-oxopentyl)-1-(5-(((2R,3S)-3-(((benzyl ox y)carbonyl)amino)-4-oxobutan-2-yl)oxy)-5-oxopentyl)-1H-imidazol-3-ium hexafluorophosphate 4. White powder, m.p. = 97-100 °C.

¹H NMR (600 MHz, DMSO-d₆): 0.65 (d, J = 6.5 Hz, 3H, CH₃); 0.70 (d, J = 6.5 Hz, 3H, CH₃); 0.87 (d, J = 6.5 Hz, 3H, CH₃); 1.38-1.45 (m, 2H, CH₂); 1.48-1.55 (m, 2H, CH₂); 1.69-1.78 (m, 3H, CH₂ + CH(CH₃)₂); 1.78-1.85 (m, 2H, CH₂); 2.13-2.24 (m, 2H, CH₂); 2.40 (t, J = 7.3 Hz, 2H, CH₂); 3.99 (t, J = 8.2 Hz, 1H, CH); 4.11 (t, J = 6.9 Hz, 2H, CH₂); 4.18 (t, J = 6.9 Hz, 2H, CH₂); 4.84 (m, 1H, CH); 4.89 (d, J = 9.5 Hz, 1H, CH); 5.04 (2H, CH₂ AB system, Jₙ₁=12.66 Hz); 5.10 (s, 2H, CH₂); 5.64 (s, 1H, OH); 7.08 (t, J = 7.2 Hz, 1H, CH); 7.13-7.21 (m, 3H, CH₃); 7.26-7.41 (m, 12H, CH); 7.46-7.55 (m, 4H, CH); 7.60 (d, J = 10.0 Hz, 1H, NH); 7.71 (d, J = 8.9 Hz, 1H, NH); 7.79 (d, J = 5.0 Hz, 2H, NCHCHN); 9.15-9.24 (m, 1H, NCHN);

¹³C NMR (125.76 MHz, DMSO-d₆): 16.6, 18.2, 21.3, 21.4, 23.2, 29.05, 29.15, 33.1, 33.2, 48.9, 58.2, 59.2, 65.9, 69.8, 81.3, 122.9, 125.7, 125.8, 126.6, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 128.9, 136.4, 136.6, 137.5, 146.5, 147.7, 156.5, 169.3, 172.1, 172.9;

Elemental analysis calcd for C₉₉H₇₉F₆N₄O₈P: C, 60.24; H, 6.09; N, 5.73; found: C, 60.06; H, 6.14, N, 5.79.
ON N O

ON NCbz

NH

OH

PF

6

\text{VVCatPr} \quad \text{VVCatPr DMSO–D6 nmr H H r.t.}
The spectrum shows a 13C NMR spectrum of a compound labeled as 'ZSGN VVCatPr'. The spectrum is recorded in D6 DMSO at room temperature (r.t.). The peaks are labeled with chemical shifts in ppm.
Synthesis and characterization of 1c

1-(5-{[(2R,3S)-3-amino-4-{[(S)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl]amino}-4-oxobutan-2-yl]oxy}-5-oxopentyl)-3-(4-carboxybutyl)-1H-imidazol-3-ium hexafluorophosphate

The 5% Pd/C (50 mg) was added to a solution of 4 (120 mg, 0.12 mmol) in freshly distilled methanol (3 mL) and the reaction mixture was vigorously stirred under H₂ atmosphere (~1 bar) for 5 h at ambient temperature. The reaction mixture was filtered and evaporated under reduced pressure (20 Torr). The residue was dried in vacuo (2 Torr) at 40 °C for 1 h to afford 89 mg (96%) of 1c.

Light yellow powder, m.p. = 89-91 °C,

¹H NMR (600 MHz, DMSO-d₆): 0.58 (d, J = 3.2 Hz, 3H, CH₃); 0.68-0.73 (m, 3H, CH₃); 0.80-0.90 (m, 3H, CH₃); 1.40-1.53 (m, 4H, 2xCH₂); 1.62-1.74 (m, 1H, CH-i-Pr); 1.71-1.87 (m, 4H, 2xCH₂); 2.18 (t, J = 7.1 Hz, 2H, CH₂); 2.28 (t, J = 7.2 Hz, 2H, CH₂); 3.64-3.72 (m, 1H, CH₃COH); 3.98 (t, J = 7.4 Hz, 1H, CH(NH)CONH); 4.13-4.24 (m, 4H, 2xCH₂); 4.50-4.62 (m, 1H, CH(i-Pr)NH); 4.87 (d, J = 9.5 Hz, 1H, OH); 5.67 (s, 1H, OH); 7.06-7.23 (m, 4H, CH); 7.29 (t, J = 7.7 Hz, 2H, CH); 7.42 (d, J = 10.1 Hz, 1H, NH); 7.49 (t, J = 6.7 Hz, 4H, CH); 7.81 (d, J = 11.7 Hz, 2H, NCHCHN); 7.94 (d, J = 8.4 Hz, 1H, NH); 9.24 (s, 1H, NCHN); 12.08 (s, 1H, COOH);

¹³C NMR (): 18.2, 19.9, 21.5, 22.2, 23.3, 28.9, 29.1, 29.3, 29.6, 33.3, 34.6, 49.0, 49.1, 57.9, 59.4, 66.1, 81.3, 122.9, 125.6, 126.0, 126.6, 128.1, 128.5, 136.4, 146.7, 170.8, 172.1, 174.5.

HRMS (ESI): m/z calcd. for C₃₄H₄₇N₄O₆⁺: 607.3490, found: 607.3493
Display Report

Analysis Info

Analysis Name: D:\Data\Chizhov\Zlotin\Gerasimchuk\vcat-2.d
Method: tune_wide.m
Sample Name: ZSGN VVCat-2
Comment: CH3OH 100 %, dil. 200, no calibrant added

Acquisition Parameter

Source Type: ESI  Ion Polarity: Positive
Focus: Not active  Set Capillary: 4500 V
Scan Begin: 50 m/z  Set Dry Gas: 4.0 l/min
Scan End: 3000 m/z  Set Dry Heater: 180 °C
Set Divert Valve: Waste
Set Nebulizer: 0.4 Bar

Intens. x10^6

607.3493

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607.3493

617.5125

621.3653

629.3310

635.3764

C34H4T4N4O6, M+Na, 629.33

C34H46N4O6, M+Na, .62933

Bruker Compass DataAnalysis 4.0  printed: 21.12.2015 18:24:42  Page 1 of 1
General procedure for syn-aldol reaction
Aldehyde 6a-i (0.066 mmol) and catalyst 1c (7.5 mg, 0.01 mmol) were dissolved in dry toluene (90 µL). Then, ketone 5a-c (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 7a-l were measured by ¹H NMR spectroscopy. The ee values of aldol products 7 were determined by chiral HPLC column (Daicel Chiralpak AD-H).

General procedure for recycling experiment
After 24 h, the mixture of hydroxyacetone (5a) (74 mg, 70 µl, 1 mmol), 2-chlorobenzaldehyde (6d) (46.8 mg, 0.33 mmol), catalyst 1c (37.5 mg, 0.05 mmol) and toluene (0.45 mL) was gently evaporated (40 °C, 8 mbar). Product 7d and unchanged starting compounds were carefully extracted from the residue by Et₂O (3 x 0.7 mL). Fresh portions of reagents and toluene were added to the remaining catalyst 1c and catalytic procedure was re-performed as described above.
Characterization of (3R,4S)-4-(2,4-dimethoxyphenyl)-3,4-dihydroxybutan-2-one (7i)

$^1$H NMR (500 MHz, CDCl$_3$): 2.27 (s, 3H, CH$_3$), 3.82 (d, 6H, (OCH$_3$)$_2$), 4.41 (s, 1H), 5.31 (s, 1H), 6.42-6.60 (m, 2H, Ar), 7.31 (m, 1H, Ar)

$^{13}$C NMR (125 MHz, CDCl$_3$): 26.4, 55.8, 56.0, 69.5, 71.5, 80.2, 80.4, 99.0, 104.8, 104.9, 121.5, 128.1, 129.0, 157.3, 161.13, 208.86

HRMS (ESI) m/z calcd. for [C$_{12}$H$_{16}$O$_5$+Na]: 263.0890; found: 263.0890

HPLC traces (Chiralpak AD-H, 1 ml/min, hexane:i-PrOH=80:20, λ=254 nm):
© Zelinsky Institute of Organic Chemistry, Moscow; Bruker DRX500 SF=500.13 MHz {1H} S=64K SW=8993 O1=5751 PW=16.0 AQ=3.636 RD=0.10 NS=1 SR=4.34 TE=296K 10 November 2016 Oper: Fakhrutdinov A.N.; Solv: CDC3

/FROG VV24dimethoxy

VV24dimethoxy CDCl3 NMR 1H r.t.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} &
\end{align*}
\]
Issue in Honor of Prof. Oleg A. Rakitin

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© Zelinsky Institute of Organic Chemistry, Moscow; Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=30350 O1=13205 PW=12.0 AQ=0.809 RU=0.80 NS=32 SR=72.62 TE=296K 10 November 2016 Opr: Fakhrotdinov A.N.; Solv: CDCl3

/FOG VV24dimethoxy

VV24dimethoxy CDCl3 NMR 13C r.t.

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
HPLC traces for 7

Chiralpak AD-H, 1.0 ml/min, Hexane:PrOH = 70:30, λ =254 nm

Chiralpak AD-H, 1 ml/min, Hexane:PrOH = 85:15, λ =280 nm
Chiralpak AD-H, 1ml/min, Hexane:iPrOH = 95:5, λ =220 nm

Chiralpak AD-H, 0.6ml/min, Hexane:iPrOH = 90:10, λ =254 nm
Chiralpak AD-H, 1.0 ml/min, Hexane:iPrOH = 85:15, λ = 254 nm

Chiralpak AD-H, 1 ml/min, Hexane:iPrOH = 96:4, λ = 254 nm, 24 °C
Chiralpak AS-H, 1 ml/min, Hexane:iPrOH = 92:8, λ =220 nm

![Chiralpak AS-H chromatogram](image1)

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Chiralpak AD-H, 1 ml/min, Hexane:iPrOH=80:20, λ=254 nm

![Chiralpak AD-H chromatogram](image2)

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References