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(*S*)-Threonine/α,α-(*S*)-diphenylvalinol-derived chiral ionic liquid: an immobilized organocatalyst for asymmetric *syn*-aldol reactions

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ABSTRACT

Chiral ionic liquids containing (*S*)- or (*R*)-threonine amide and α,α-(*S*)-diphenylvalinol units were synthesized In the presence of the (*S*)-threonine-derived catalyst reactions between ketones with secondary carbon atom(s) at the α-position with respect to the carbonyl group and aromatic (heteroaromatic) aldehydes afforded the corresponding *syn*-aldols in high yields (up to 99%) and with high diastereo-(*syn*/*anti* up to 97:3) and enantioselectivity (up to 99% ee), which was maintained over three reaction cycles.

1. Introduction

Asymmetric aldol reactions are widely used for the formation of the carbon–carbon bonds in organic compounds.[1] These reactions are often carried out in the presence of chiral organocatalysts, in particular (*S*)-proline,[2] (*S*)-proline amide,[3] sulfonylamides,[4] proline-containing di- and tripeptides[5] and some others, with high diastereo- and enantioselectivity. As a rule, the major reaction products have *anti*-configuration, whereas *syn*-aldols are formed exclusively in native aldolase catalyzed aldol reactions.[6]

Recently, it was found that some primary α-amino acid-[7] or primary amine-derived[8] organocatalysts direct, like enzymes, asymmetric aldol reactions toward the formation of *syn*-products. Among them, α-amino acid amides **A**, containing a chiral β-aminoalcohol fragment within the amide unit are the most efficient ones (Fig. 1).[9]

The synthesis of catalysts **A**, containing several chiral centers in the molecule, is rather complicated and/or expensive, which makes their regeneration desirable. Very recently, we discovered that the modification of proline amides with ionic groups, in particular with imidazolium cation and PF_6^- anion, opens up a convenient way to their immobilization.[10] It might be expected that application of this approach to primary α-amino acid amides would lead to the development of immobilized organocatalysts for *syn*-aldol reactions. As far as we know, organocatalysts of this type have not been prepared so far.

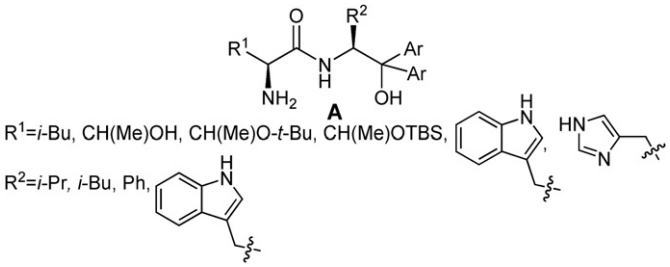

Fig. 1. Known organocatalysts of *syn*-aldol reactions.

2. Results and discussion

To verify this hypothesis, we synthesized (2*S*,3*R*)-threonine **1a** and (2*R*,3*S*)-threonine **1b** amides, bearing the α,α-(*S*)-diphenylvalinol fragment along with the ionic group. The synthetic scheme included the reaction of commercially available *N*-Cbz-protected amino acids **2a**,**b** with α,α-(*S*)-diphenylvalinol in the presence of $ClCO_2Et/Et_3N$, esterification of the corresponding amides **3a**,**b** under the action of 5-bromovaleric acid and DCC/DMAP, subsequent reaction of esters **4a**,**b** with methyl-1*H*-imidazole, followed by metathesis of the anion in bromides **5a**,**b** and deprotection (H_2–5% Pd/C) of the amino group in hexafluorophosphates **6a**,**b**. Salts **1a** and **1b** melt at 110 °C and 96 °C, respectively, and can be described as chiral ionic liquids (Scheme 1).

We studied the catalytic properties of (*S*)-threonine-derived chiral salt **1a** in a model aldol reaction between hydroxyacetone **7a**

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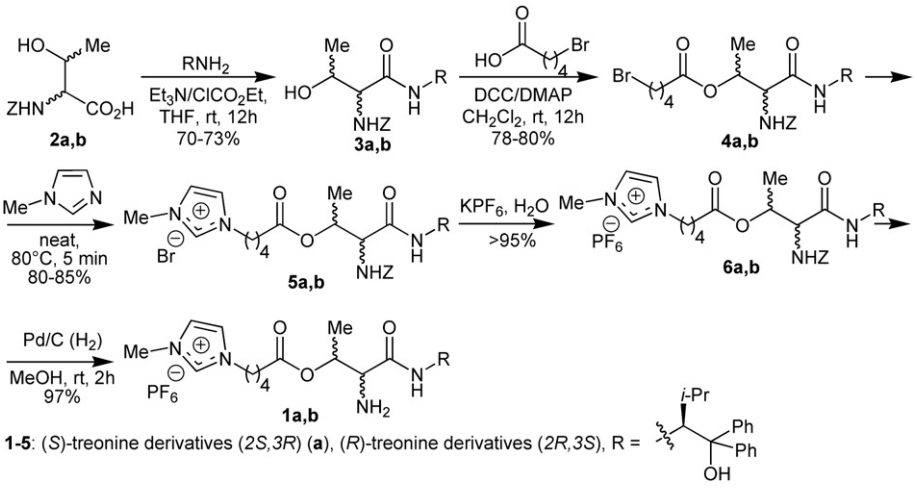
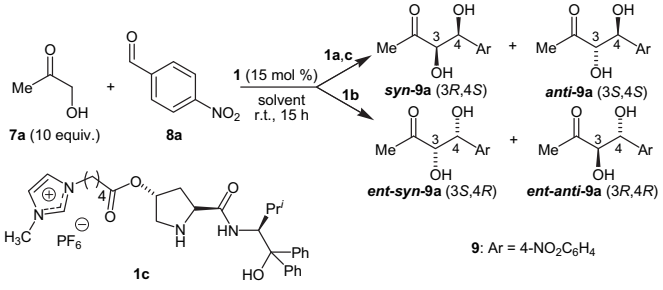


Scheme 1. Synthesis of (*S*)- or (*R*)-threonine-derived catalysts **1a**,**b** modified with ionic groups.

(10 equiv) and 4-nitrobenzaldehyde **8a** at ambient temperature in CH_2Cl_2, THF, toluene, NMP, water or under neat conditions. The amount of organocatalyst **1a** was 15 mol % with respect to aldehyde **8a**. Under the studied conditions *syn*-aldol **9a** formed as the major product (*syn*/*anti*>9:1). The enantiomeric excess of the compound *syn*-**9a** was 92–96% ee irrespective of the solvent. However, the product yield was influenced by the solvent nature: it was poor (10–45%) in CH_2Cl_2, THF, NMP or water (Table 1, entries 1–4) and rose to 99% in toluene or under neat conditions (Table 1, entries 5, 6). Lowering the temperature to 4 °C or ketone **7a** excess to 5 equiv resulted in a decrease of the reaction rate but scarcely effected selectivity (Table 1, entries 7, 8). The reaction between compounds **7**a and **8**a in the presence of (*R*)-threonine-derived organocatalyst **1b** (15 mol %) under optimal conditions (PhMe, rt) gave the aldol *ent*-**9a** in 99% yield (Table 1, entry 9), however, diastereo- (*syn*/*anti* 76/24) and enantioselectivity (−14% ee) were lower than in the respective reaction catalyzed by the isomer **1a**. The presence of the primary amino acid fragment in catalysts **1a** and **1b** is crucial for the *syn*-diastereoselectivity: *anti*-aldol **9a** was the major product when the reaction between compounds **7a** and **8a** was carried out in the presence of immobilized catalyst **1c**[10c] (15 mol %) bearing (*S*)-proline instead of (*S*)-threonine unit (Table 1, entry 10).

Next, we applied catalyst **1a** in asymmetric aldol reactions between hydroxyacetone (**7a**) and aromatic (heteroaromatic) aldehydes **8a**–**j**. In all the cases, the corresponding aldols **9a**–**o** were obtained. High yields (90–99%) were achieved after 24 h in the reactions of aldehydes **8a**–**f**, bearing electron-withdrawing groups on the aromatic ring (Table 2, entries 1–6) and in the reaction of

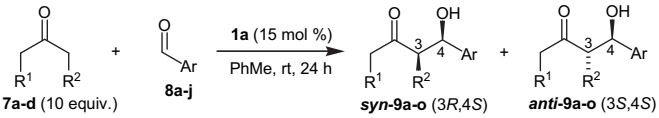
Table 1
Asymmetric aldol reactions between compounds **7a** and **8a** in the presence of organocatalysts **1a**, **1b** or **1c**: optimization of reaction conditions



Entry	Solvent	Catalyst	Yield of **9** %[a]	dr (*syn*/*anti*)[b]	ee (*syn*) %[c]
1	CH_2Cl_2	**1a**	**9a**, 45	93/7	96
2	THF	**1a**	**9a**, 10	93/7	94
3	NMP	**1a**	**9a**, 10	92/8	92
4	H_2O	**1a**	**9a**, 9	93/7	94
5	neat	**1a**	**9a**, 99	90/10	92
6	PhMe	**1a**	**9a**, 99(91[d])	93/7(80/20[d])	94(80[d])
7[e]	PhMe	**1a**	**9a**, 75	94/6	93
8[f]	PhMe	**1a**	**9a**, 80	92/8	92
9	PhMe	**1b**	*ent*-**9a**, 99	76/24	−14
10	PhMe	**1c**	**9a**, 90	24/76	70[g]

[a] Total yield of a mixture of *syn*- and *anti*-isomers after column chromatography on silica gel.
[b] ^{1}H NMR spectroscopic data ($J_{H^3-H^4}$ *syn* 2.6 Hz, $J_{H^3-H^4}$ *anti* 5.0 Hz).
[c] HPLC (Daicel Chiralpak AD, Hexane/Isopropanol=9:1, Flow rate=0.5 mL/min, 254 nm): t_R=62.5 min (minor−3*S*,4*R*-*syn*-**9a**), 93.0 min (major−3*R*,4*S*-*syn*-**9a**).
[d] Data according to Ref. 9a.
[e] The reaction was carried out at 4 °C.
[f] The amount of **7a** was 5 equiv with respect to **8a**.
[g] The ee value of *anti*-**9a** is given.

Table 2
IL **1**a-catalyzed asymmetric aldol reactions between compounds **7** and **8**[a]



7: R^1 = H, R^2 = OH (**a**), OMe (**b**), Me (**c**); R^1 = R^2 = OH (**d**)

Entry	9	R^1	R^2	Ar	Yield of **9** %[b]	dr (*syn*/*anti*)[c]	ee (*syn*) %[d]
1	**a**	H	OH	4-$NO_2C_6H_4$	99 (91[e])	93/7 (80/20[e])	94 (80[e])
2	**b**	H	OH	2-$NO_2C_6H_4$	94 (92[f], 91[g], 85[h])	97/3 (>95/5[f], 99/1[g], 97/3[h])	97 (98[f], 99[g], 98[h])
3	**c**	H	OH	2-ClC_6H_4	96 (91[f], 99[g])	97/3 (94/6[f], 88/12[g])	97 (97[f], 92[g])
4	**d**	H	OH	4-FC_6H_4	99	86/14	92
5	**e**	H	OH	4-$MeO_2CC_6H_4$	95 (95[f])	93/7 (93/7[f])	95 (95[f])
6	**f**	H	OH	4-$OHCC_6H_4$	90	80/20	99
7[i]	**g**	H	OH	4-$MeOC_6H_4$	79 (50[g])	96/4 (94/6[g])	96 (93[g])
8	**h**	H	OH	3-$PhOC_6H_4$	48	94/6	94
9	**i**	H	OH	2-Naphthyl	60	95/5	87
10	**j**	H	OH	2-Thienyl	99	95/5	98
11	**k**	H	OMe	4-$NO_2C_6H_4$	99	84/16	99
12	**l**	H	OMe	2-ClC_6H_4	98	95/5	97
13	**m**	H	OMe	2-Thienyl	99	95/5	96
14[i]	**n**	H	Me	4-$NO_2C_6H_4$	46	75/25	86
15[j]	**o**	OH	OH	4-$NO_2C_6H_4$	40	90/10	92

[a] Unless otherwise specified, reactions were carried out with **7** (1.3 mmol), **8** (0.13 mmol), and the toluene (0.2 mL).
[b] Total yield of a mixture of *syn*- and *anti*-isomers after column chromatography on silica gel.
[c] ^{1}H NMR spectroscopic data.
[d] HPLC data (Chiralcel AD, eluent *n*-hexane/*i*-PrOH 7/3, 0.7 mL/min, 254 nm) for purified compounds.
[e] Data according to Ref. 9a.
[f] Data according to Ref. 9c.
[g] Data according to Ref. 8b.
[h] Data according to Ref. 8a.
[i] Reaction period was 50 h.
[j] Dihydroxyacetone **7d** was generated in situ from corresponding dimer in the presence of AcOH (15 mol %) and the reaction period was 60 h.

2-thiophene aldehyde **8j** (Table 2, entry 10). Interestingly, only one of two aldehyde groups in terephthalaldehyde **8f** took part in the reaction (Table 2, entry 6). 4-Methoxybenzaldehyde (**8g**) and polynuclear aromatic aldehydes **8h**,**i** were found to be less active under the conditions studied: yields of respective aldols **9h**,**i** after 24 h were 48–60% and the aldol **9g** was obtained in 79% yield after 48 h (Table 2, entries 7–9). The scope of the donor ketones is not limited by hydroxyacetone **7a**. Methoxyacetone (**7b**) also reacted with aldehydes **8** under the studied conditions yielding the respective aldols **9k**–**m** in nearly quantitative yields (Table 2, entries 11–13). Ethyl methylketone (**7c**) and 1,3-dihydroxyacetone (**7d**), which was generated in situ from commercially available 1,3-dihydroxyacetone dimer in the presence of AcOH (15 mol %) were less active in the studied reactions. Moderate yields of corresponding aldols **9n**,**o** were achieved after 50–60 h, however, the *syn*:*anti* ratio and ee values of products **9n**,**o** were rather high (Table 2, entries 14, 15).

According to ^{1}H NMR spectroscopic data ($J^{3,4}_{H-H\ syn}$ 0–4 Hz, $J^{3,4}_{H-H\ anti}$=5–10 Hz) the *syn*/*anti* diastereomeric ratio (dr) of aldols **9a**–**o** was high (≥75:25) irrespective of the aldehyde structure. Moreover, the ee values of the major *syn*-isomers were similar to or even higher than those under the influence of the most efficient primary α-amino acid-derived catalysts **A**.[9] The absolute (3*R*,4*S*)-configuration was assigned to the major enantiomers of aldols **9** based on HPLC-analysis of the product *syn*-**9a** [Chiralcel AD, eluent *n*-hexane/*i*-PrOH 9/1, 0.5 mL/min, retention times: 62.5 min (minor–3*S*,4*R*), 93.0 min (major–3*R*,4*S*)] and comparison of the results with available HPLC-data for both enantiomers of this compound.[7a,8a] This assignment was in accordance with optical rotations of *syn*-aldols **9a** ($[\alpha]_D^{20}$ +39.0), **9b** ($[\alpha]_D^{20}$ −142.0), **9c** ($[\alpha]_D^{20}$ +37.2), their signs were opposite to the reported rotation signs for their (3*S*,4*R*)-antipodes[8b] under similar measurement conditions (*c* 1, CH_3OH).

The feasibility of recycling of catalyst **1a** was demonstrated in the asymmetric aldol reaction between compounds **7a** and **8a**. After the reaction completed, aldol **9a** was extracted with diethyl ether and replaced with fresh portions of starting compounds **7a** and **8a** in toluene. Product yield and reaction diastereo- and enantioselectivity retained over three reaction cycles (Table 3). However, the reaction period increased from 24 h in the first cycle to 4 and 7 days in the second and in the third cycles, respectively, and in the fourth iteration the yield of aldol **9a** did not exceed 20% over a week. The catalyst deactivation was not caused by its 'washing out' during the working-up procedure. In contrast, the mass of recovered matter increased by 15–20% in each subsequent cycle presumably due to the formation of by-products incorporating the catalyst. The reaction rate became somewhat higher after the addition of AcOH (15 mol %). Hence, we assume that the acid returned part of the poisoned catalyst to the catalytic cycle.

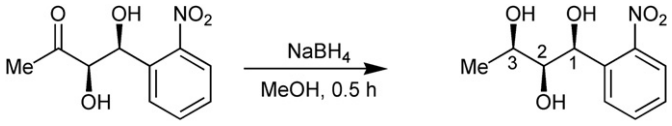
Table 3
Recycling of the catalyst **1a** in the reaction between compounds **7a** and **8a**[a]

Cycle	Time, d[b]	Yield of **9a** %	dr (*syn*/*anti*)	ee (*syn*) %
1	1(1)	99 (98)	93/7 (92/8)	94 (92)
2	4 (2)	98 (96)	92/8 (91/9)	93 (92)
3	7 (5)	98 (94)	94/6 (92/8)	94 (91)
4	7	20	93/7	93

[a] Reactions were carried out under conditions specified in Table 2; After the indicated time the catalyst was separated from the products by addition of ether (see Experimental section) and reused.
[b] Reaction period in the presence of AcOH (15 mol %) is given in brackets.

The prepared compounds are valuable intermediates for the synthesis of polyols with *syn*-configuration of hydroxy groups, which are structural units of carbohydrates and some other natural compounds.[11] The synthetic utility of *syn*-aldols **9** was

demonstrated by the reduction of the aldol **9b** to the triol **10** with sodium borohydride (Scheme 2). Despite of the absence of chiral catalyst, the reaction was stereoselective affording all-*syn*-1-(2-nitrophenyl)butane-1,2,3-triol **10** as the major product. The (1*S*,2*R*,3*R*)-configuration was assigned to compound **10** based on the configuration of starting aldol **9b** and on the identity of its diastereomeric composition with the reported data.[8a] The 1*S*/1*R*-ratio for compound **10** was 96/4 (^{1}H NMR spectroscopic data) in accordance with that in the aldol **9b**.



9b **1*S*,2*R*,3*R*-10**

Scheme 2. Reduction of **9b** to *syn*, *syn*-triol **10**.

3. Conclusion

In conclusion, we have synthesized for the first time an immobilized organocatalyst for asymmetric *syn*-aldol reactions by incorporating (*S*)-threonine and α,α-(*S*)-diphenylvalinol units into chiral ionic liquid. In the presence of this catalyst ketones bearing secondary carbon atom(s) at the α-position with respect to the carbonyl group reacted with aromatic (heteroaromatic) aldehydes affording the respective *syn*-aldols in high yields (up to 99%) and with high diastereo- (*syn*/*anti* up to 97:3) and enantioselectivity (up to 99% ee), which was maintained over 3 reaction cycles. The optimization of the catalyst structure aiming at the extension of its operation period is currently under way in our laboratory.

4. Experimental

4.1. General

NMR ^{1}H and ^{13}C spectra were recorded with Bruker AM 300 instrument in $CDCl_3$, DMSO-d_6 and acetone-d_6. Chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si or $CDCl_3$, respectively. High resolution mass spectra (HRMS) were measured on a Bruker microTOF II instrument using electrospray ionization (ESI).[12] The measurements were done in a positive ion mode (interface capillary voltage−4500 V) or in a negative ion mode (3200 V); mass range from *m*/*z* 50 to *m*/*z* 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solution in methanol (flow rate 3 μL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180 °C. IR spectra (KBr pellets) were recorded with a Specord M82 instrument. Specific optical rotations $[\alpha]_D^{20}$ were measured with a Jasco DIP-360 instrument at 589 nm. Silica gels 0.060−0.200 and 0.035−0.070 nm (Acros) were used for column chromatography. Solvents were purified by standard methods.

4.2. Catalysts preparation

*4.2.1. 2-Hydroxy-1-{[1-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-propyl}-carbamic acid benzyl esters (**3a**) and (**3b**).* A solution of ethylchloroformate (1.51 mL, 15.8 mmol) in THF (10 mL) was added dropwise to a stirred solution of (*S*)- or (*R*)-*N*-(carbobenzyloxy)threonine **2a** or **2b** (4.0 g, 15.8 mmol) and Et_3N (2.21 mL, 15.8 mmol) in THF (20 mL) at 0 °C for 15 min. After 30 min, α,α-(*S*)-diphenylvalinol (16.0 mmol, 3.6 g) was gradually added (15 min) to the mixture. The resulting solution was stirred at 0 °C for 1 h, kept at ambient temperature for 16 h and then diluted with ethyl acetate (30 mL). By-product $Et_3N{\cdot}HCl$ was filtered off, the filtrate was evaporated under reduced pressure and the residue was washed with hexane/Et_2O 3/1 (2×10mL). The resulting white solid was dried in vacuo (0.5 Torr) at 50 °C for 2 h to afford amides **3a** or **3b**.

Compound **3a**: Yield 5.40 g (70%) as colorless solid, mp 120−122 °C; $[\alpha]_D^{26}$ −48.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.52 (m, 4H, Ar), 6.96−7.44 (11H, Ar, 1H, N*H*), 5.91 (d, *J*=8.1 Hz, 1H, N*H*), 5.15 (m, 1H, C*H*O), 5.10 (s, 2H, CH_2CO), 4.98 (d, *J*=9.5 Hz, 1H, C*H*NHCO), 4.01 (d, *J*=7.0 Hz, 1H, C*H*NH_2), 1.88 (m, 1H, C*H*$(CH_3)_2$), 0.89 (d, *J*=7.0 Hz, 3H, OCHC*H*$_3$), 0.84 (d, *J*=7.0 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ: 170.4, 156.0, 146.3, 137.1, 128.3, 128.0, 127.8, 127.7, 127.0, 126.1, 125.4, 125.2, 80.9, 65.6, 65.4, 61.4, 57.7, 28.6, 22.9, 19.4, 17.9. IR spectra (KBr, cm^{-1}): 3401, 3063, 2963, 1707, 1643, 1532, 1450, 1250, 1063, 747, 669. Elemental analysis calcd for $C_{29}H_{34}N_2O_5$: C, 71.00; H, 6.99; N, 5.71; found C, 71.12; H, 6.81; N, 5.82.

Compound **3b**: Yield 5.6 g (73%) as colorless solid, mp 132−134 °C; $[\alpha]_D^{26}$ +17.8 (*c* 1, $CHCl_3$); ^{1}H NMR (acetone-d_6) δ: 8.06 (d, *J*=8.0 Hz, 4H, Ar), 7.61−7.96 (11H, Ar), 7.58 (d, *J*=8.0 Hz, N*H*), 6.60 (br, 1H, N*H*), 5.57 (m, 1H, C*H*O), 5.53 (m, 2H, CH_2CO), 5.48 (m, 1H, C*H*NHCO), 4.12 (m, 1H, C*H*NH_2), 2.26 (m, 1H, C*H*$(CH_3)_2$), 1.51 (d, *J*=6.2 Hz, 3H, OCHC*H*$_3$), 1.38 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ: 169.4, 154.2, 146.3, 137.1, 128.3, 128.0, 127.8, 127.8, 127.0, 126.1, 125.4, 125.2, 81.3, 65.6, 65.4, 61.4, 57.7, 28.6, 22.9, 19.4, 17.9. IR spectra (KBr, cm^{-1}): 3400, 3060, 2965, 1709, 1645, 1530, 1453, 1255, 1066, 749, 670. Elemental analysis calcd for $C_{29}H_{34}N_2O_5$: C, 71.00; H, 6.99; N, 5.71; found C, 71.28; H, 6.84; N, 5.86.

*4.2.2. 5-Bromopentanoic acid 2-benzyloxycarbonylamino-2-[1-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-1-methyl-ethyl esters (**4a**) and (**4b**).* A mixture of amide **3a** or **3b** (5.0 g, 10.2 mmol), 5-bromovaleric acid (1.84 g, 10.2 mmol), DCC (2.10 g, 10.2 mmol), and DMAP (cat.) in CH_2Cl_2 (30 mL) was stirred at 5 °C for 12 h. The precipitate was filtered off and washed with CH_2Cl_2 (3×5 mL). The combined organic extracts were evaporated, the residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 3/1) to afford ester **4a** or **4b**.

Compound **4a**: Yield 5.3 g (80%) as colorless oil, $[\alpha]_D^{26}$ −21.25 (*c* 1, $CHCl_3$); R_f=0.31; ^{1}H NMR ($CDCl_3$) δ: 7.60−7.15 (m, 15H, Ar), 6.75 (d, *J*=7.0 Hz, 1H, N*H*), 5.60 (d, *J*=9.9 Hz, 1H, N*H*), 5.30−5.05 (s, 2H, CH_2CO, 1H, C*H*), 5.01 (d, *J*=9.8 Hz, 1H, C*H*), 4.18 (m, 1H, C*H*NH_2), 3.32 (t, *J*=6.3 Hz, 2H, CH_2Br), 2.60 (br, 1H, O*H*), 2.22 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 1.70 (m, 1H, C*H*; 2H, CH_2), 1.80 (m, 2H, CH_2; 1H, C*H*$(CH_3)_2$), 0.85−0.76 (m, 3H, OCHC*H*$_3$; 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ: 172.0, 168.8, 155.2, 147.4, 146.2, 137.1, 128.5−125.4 (Ar), 81.0, 69.5, 65.8, 58.9, 57.9, 34.7, 31.9, 28.7, 23.1, 23.0, 17.9, 16.6. IR spectra (KBr, cm^{-1}): 3464, 3321, 3062, 2936, 1726, 1648, 1533, 1449, 1239, 1064, 747, 699. Elemental analysis calcd for $C_{34}H_{41}BrN_2O_6$: C, 62.48; H, 6.32; N, 4.29; found C, 62.23; H, 6.24; N, 4.41.

Compound **4b**: Yield 5.2 g (78%) as colorless oil, $[\alpha]_D^{26}$ −21.45 (*c* 1, $CHCl_3$); R_f=0.34; ^{1}H NMR (acetone-d_6) δ: 7.17−7.51 (15H, Ar). 7.14 (d, *J*=7.0 Hz, 1H, N*H*), 6.67 (d, *J*=9.9 Hz, 1H, N*H*), 5.40 (m, 1H, C*H*), 5.32 (m, 1H, C*H*NH_2), 5.0 (m, 2H, CH_2CO), 4.12 (dd, J^1=4.9 Hz, J^2=12.8 Hz, 1H), 3.35 (t, *J*=6.3 Hz, 2H, CH_2Br), 2.78 (br, 1H, O*H*), 1.86 (m, 1H, C*H*$(CH_3)_2$), 1.80 (m, 2H, CH_2CH_2), 1.63 (m, 2H, CH_2CH_2), 1.24 (d, *J*=6.2 Hz, 3H, OCHC*H*$_3$), 0.86 (m, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ: 171.0, 168.6, 156.2, 146.1, 145.3, 128.6−125.3 (Ar), 82.2, 69.6, 67.3, 58.8, 58.0, 33.0, 31.9, 28.9, 23.3, 22.7, 17.4, 16.8. IR spectra (KBr, cm^{-1}): 3466, 3319, 3060, 2933, 1728, 1650, 1530, 1451, 1242, 1065, 749, 701. Elemental analysis calcd for $C_{34}H_{41}BrN_2O_6$: C, 62.48; H, 6.32; N, 4.29; found C, 62.31; H, 6.19; N, 4.37.

*4.2.3. 1-(4-{2-Benzyloxycarbonylamino-2-[1-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-1-methyl-ethoxycarbonyl}-butyl)-3-methyl-3H-imidazol-1-ium bromides (**5a**) and (**5b**).* A mixture of compound **4a** or **4b** (5.00 g, 7.65 mmol) and 1-methyl-1*H*-imidazole (2.46 g, 30 mmol) was heated at 80 °C for 5 min, cooled to 20 °C and washed thoroughly with Et_2O (5×10 mL). The residue was dissolved in MeOH (3 mL), then Et_2O (30 mL) was added to the solution.

The separated oil was dried under reduced pressure (0.5 Torr) for 1 h to afford bromides **5a** or **5b**.

Compound **5a**: Yield 4.8 g (85%) as highly hydroscopic yellow solid, $[\alpha]_D^{26}$ −33.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 10.04 (s, 1H, NC*H*N), 8.09–6.98 (m, 17H, Ar; 1H, N*H*), 5.98 (d, *J*=8.2 Hz, 1H, N*H*), 5.02–4.90 (m, 2H, CH_2; 1H, C*H*; 1H, C*H*), 4.47 (m, 1H, C*H*), 4.16 (m, 2H, CH_2), 3.96 (s, 3H, CH_3), 2.26 (m, 2H, CH_2), 1.87 (m, 2H, CH_2; 1H, C*H*), 1.53 (m, 2H, CH_2), 0.98 (d, *J*=7.5 Hz, 3H, OCHCH_3), 0.78 (d, *J*=6.4 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ: 171.7, 168.9, 155.9, 147.2, 146.0, 136.9, 136.5, 128.3–122.2 (Ar), 80.8, 69.4, 65.4, 58.8, 57.8, 48.4, 35.8, 34.5, 28.6, 22.7, 21.7, 17.8, 16.1. IR spectra (KBr, cm^{-1}): 3391, 3063, 2958, 1721, 1664, 1525, 1450, 1238, 1169, 1064, 749, 702. Elemental analysis calcd for $C_{38}H_{47}BrN_4O_6$: C, 62.04; H, 6.44; N, 7.62; found C, 62.22; H, 6.35; N, 7.49.

Compound **5b**: Yield 4.5 g (80%) as highly hydroscopic yellow solid, $[\alpha]_D^{26}$ −38.84° (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 9.97 (s, 1H, NC*H*N), 7.88 (d, *J*=10.6 Hz, 1H, N*H*), 7.90–6.92 (m, 17H, Ar), 6.44 (d, J^1=7.7 Hz, 1H, N*H*), 5.17 (m, 1H, CH), 5.05 (s, 2H, CH_2CO), 5.01 (m, 1H, C*H*,), 4.44 (m, 1H, C*H*), 4.17 (m, 2H, CH_2), 3.82 (s, 3H, CH_3), 2.29 (m, 2H, CH_2), 1.83 (m, 2H, CH_2; 1H, C*H*), 1.53 (m, 2H, CH_2), 1.20 (d, J^1=6.0 Hz, 3H, CH_3), 1.01 (d, J^1=6.6 Hz, 3H, OCHCH_3), 0.80 (d, J^1=6.3 Hz, 3H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ: 171.9, 169.0, 156.3, 147.5, 145.0, 134.5, 128.6–122.1 (Ar), 82.0, 70.1, 66.7, 58.6, 49.3, 36.6, 33.3, 29.2, 28.9, 23.0, 21.0, 18.3, 16.4. IR spectra (KBr, cm^{-1}): 3390, 3060, 2959, 1723, 1665, 1528, 1451, 1240, 1170, 1062, 752, 701. Elemental analysis calcd for $C_{38}H_{47}BrN_4O_6$: C, 62.04; H, 6.44; N, 7.62; found C, 62.31; H, 6.29; N, 7.81.

*4.2.4. 1-(4-{2-Benzyloxycarbonylamino-2-[1-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-1-methyl-ethoxycarbonyl}-butyl)-3-methyl-3H-imidazol-1-ium hexafluorophosphates (**6a**) and (**6b**).* A solution of KPF_6 (1.1 g, 5.44 mmol) in water (10 mL) was added to a stirred solution of bromide **5a** or **5b** (4.0 g, 5.44 mmol) in water (10 mL). The precipitate was filtered off, washed with water (3×10 mL) and dried under reduced pressure (0.5 Torr) for 1 h.

Compound **6a**: Yield 4.2 g (96%), colorless solid, mp 156–157 °C; $[\alpha]_D^{26}$ −28.1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 9.10 (s, 1H, NC*H*N), 8.10–6.90 (m, 17H, Ar; 1H, N*H*), 6.01 (d, *J*=8.0 Hz, 1H, N*H*), 5.01–4.87 (m, 2H, CH_2; 1H, C*H*; 1H, C*H*), 4.46 (m, 1H, C*H*), 4.20 (m, 2H, CH_2), 3.96 (s, 3H, CH_3), 2.26 (m, 2H, CH_2), 1.87 (m, 2H, CH_2; 1H, C*H*), 1.53 (m, 2H, CH_2), 0.98 (d, *J*=7.0 Hz, 3H, OCHCH_3), 0.78 (d, *J*=6.3 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ: 170.1, 166.3, 155.9, 147.2, 146.0, 136.9, 136.5, 126.3–120.1 (Ar), 81.0, 70.3, 65.2, 57.8, 56.4, 43.1, 33.4, 34.6, 28.4, 21.4, 22.3, 17.6, 16.0. IR spectra (KBr, cm^{-1}): 3411, 3167, 2961, 1723, 1656, 1524, 1450, 1239, 1170, 1065, 844, 749, 703, 558. Elemental analysis calcd for $C_{38}H_{47}PF_6N_4O_6$: C, 57.00; H, 5.92; N, 7.00; found C, 56.92; H, 5.81; N, 7.11.

Compound **6b**: Yield 4.25 g (97%), colorless solid, mp 168–169 °C; $[\alpha]_D^{26}$ −36.1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 9.09 (s, 1H, NC*H*N), 8.11–6.90 (m, 17H, Ar; 1H, N*H*), 5.98 (d, *J*=8.0 Hz, 1H, N*H*), 5.01–4.87 (m, 2H, CH_2; 1H, C*H*; 1H, C*H*), 4.31 (m, 1H, C*H*), 4.18 (m, 2H, CH_2), 4.01 (s, 3H, CH_3), 2.26 (m, 2H, CH_2), 1.87 (m, 2H, CH_2; 1H, C*H*), 1.53 (m, 2H, CH_2), 0.98 (d, *J*=7.0 Hz, 3H, OCHCH_3), 0.78 (d, *J*=6.3 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ: 169.1, 165.3, 156.7, 146.3, 145.6, 137.5, 136.5, 125.3–122.1 (Ar), 82.0, 70.8, 66.0, 58.8, 56.7, 44.8, 34.1, 34.8, 28.1, 21.2, 22.4, 17.63, 15.6. IR spectra (KBr, cm^{-1}): 3412, 3166, 2963, 1727, 1655, 1521, 1452, 1241, 1172, 1068, 850, 746, 702, 560. Elemental analysis calcd for $C_{38}H_{47}PF_6N_4O_6$: C, 57.00; H, 5.92; N, 7.00; found C, 56.88; H, 5.80; N, 7.13.

*4.2.5. 1-(4-{2-Amino-2-[1-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-1-methyl-ethoxycarbonyl}-butyl)-3-methyl-3H-imidazol-1-ium hexafluorophosphates (**1a**) and (**1b**).* The obtained colorless solid **6a**,**b** (4.2 g, 5.00 mmol) was dissolved in CH_3OH (100 mL) and 5% Pd/C (300 mg) was added to the solution. The resulting suspension was stirred under H_2 (1 bar) for 2 h, filtered, the filtrate was evaporated under reduced pressure (40 Torr) and the residue was dried in vacuo (0.5 Torr) for 2 h to afford catalyst **1a** or **1b**.

Catalyst **1a**: Colorless solid, yield 3.5 g (97%), mp 110–112 °C; $[\alpha]_D^{26}$ −32.0 (*c* 1, CH_3OH); ^1H NMR (acetone-d_6) δ: 9.08 (s, 1H, NC*H*N), 7.76 (s, 2H, NC*H*CHN), 7.70 (s, 2H, NCHC*H*N), 7.60 (m, 4H, Ar), 7.44–7.03 (8H, Ar and N*H*), 5.12 (br, 1H, C*H*O), 5.00 (dd, J^1=6.23 Hz, J^2=2.2 Hz, 1H, C*H*NHCO), 4.37 (t, *J*=7.30 Hz, 2H, NCH_2CH$_2$), 4.21 (m, 1H, C*H*NH$_2$), 4.06 (s, 3H, NCH_3), 2.93 (br, 1H, O*H*), 2.34 (t, *J*=7.00 Hz, 2H, CH_2CO), 2.04 (m, 2H, CH_2CH$_2$), 1.96 (m, 1H, C*H*(CH$_3$)$_2$), 1.64 (m, 2H, CH$_2$CH_2), 0.94 (d, *J*=6.60 Hz 3H, OCHCH_3), 0.77 (dd, J^1=6.60 Hz, J^2=2.5 Hz, 6H, CHCH_3); ^{13}C NMR ($CDCl_3$) δ: 171.9, 170.5, 147.4, 146.6, 128.1, 127.8, 126.2, 125.7, 125.4, 123.7, 122.4, 81.1, 71.00, 59.1, 57.6, 48.6, 35.8, 32.9, 28.9, 28.6, 23.0, 22.03, 18.07. IR spectra (KBr, cm^{-1}): 3413, 2962, 1637, 1522, 1450, 1171, 843, 751, 707, 558. Elemental analysis calcd for $C_{30}H_{41}F_6N_4O_4P$: C 54.05; H 6.20; N 8.40; P 4.65. Found C 54.28; H 6.11; N 8.17; P 4.89. HRMS: $C_{30}H_{41}N_4O_4$ calcd 521.3122, found 521.3116. HRMS: $C_{30}H_{41}N_4O_4$ calcd 521.3122, found 521.3102.

Catalyst **1b**: Yield 3.5 g (97%), mp 96–98 °C $[\alpha]_D^{26}$ −11.1 (*c* 1, CH_3OH); ^1H NMR (DMSO-d_6) δ: 9.08 (s, 1H, NC*H*N), 7.70 (s, 2H, NC*H*CHN), 7.68 (s, 2H, NCHC*H*N), 7.47 (m, 4H, Ar), 7.34–7.00 (8H, Ar and N*H*), 4.85 (m, 1H, C*H*O), 4.53 (d, *J*=5.10 Hz, 1H, C*H*NHCO), 4.16 (t, *J*=6.80 Hz, 2H, NCH_2CH$_2$), 3.90 (m, 1H, C*H*NH$_2$), 3.84 (s, 3H, NCH_3), 2.17 (t, *J*=7.10 Hz, 2H, CH_2CO), 1.75 (m, 3H, CH_2CH$_2$, C*H*(CH$_3$)$_2$), 1.44 (m, 2H, CH$_2$CH_2), 0.85 (d, *J*=6.40 Hz 3H, OCHCH_3), 0.66 (d, *J*=6.80 Hz, 3H, CHCH_3), 0.57 (d, *J*=5.50 Hz, 3H, CHCH_3); ^{13}C NMR ($CDCl_3$) δ: 172.1, 169.5, 145.4, 144.3, 124.6, 126.4, 126.2, 123.9, 122.8, 122.6, 122.4, 82.3, 72.2, 60.3, 58.6, 50.7, 35.8, 32.9, 28.9, 28.4, 23.5, 21.0, 16.3. IR spectra (KBr, cm^{-1}): 3411, 2963, 1638, 1520, 1452, 1174, 845, 750, 704, 560. Elemental analysis calcd for $C_{30}H_{41}F_6N_4O_4P$: C 54.05; H 6.20; N 8.40; P 4.65. Found C 53.77; H 6.35; N 8.61; P 4.72. HRMS: $C_{30}H_{41}N_4O_4$ calcd 521.3122, found 521.3117.

4.3. General procedure for the aldol reaction

Ketone **7** (1.30 mmol) and aldehyde **8** (0.13 mmol) and AcOH (0.02 mmol, if specified) were added to a suspension of the catalyst **1a**, **1b** or **1c** (0.02 mmol) in toluene (0.2 mL). The reaction mixture was stirred at ambient temperature for the indicated time (TLC-monitoring) (Tables 1–3). The solvent was evaporated under reduced pressure and the residue was extracted with Et_2O (3×1 mL). The combined extracts were evaporated in vacuo affording aldols **9**, which were purified by column chromatography on silica gel. Yields of compounds **9** are given in Tables 1–3. Optical rotations and ^1H NMR data of compounds **9a**–**c**,[9a,c] **9e**,[9c] **9g**,[8b] **9k**,[13] **9l**,[13] **9n**,[8e] and **9o**[8b] were identical to reported in the literature. Characteristics of newly synthesized compounds are given below.

*4.3.1. (3R,4S)-4-(4-fluorophenyl)-3,4-dihydroxybutan-2-one (**9d**).* Colorless oil; $[\alpha]_D^{20}$ +26.3 (*c* 1, MeOH); ^1H NMR ($CDCl_3$): δ=7.41 (m, 2H, Ar), 7.08 (t, *J*=9.2 Hz, 2H, Ar), 5.0 (d, *J*=3.6 Hz, 1H, C*H*OH), 4.37 (d, *J*=3.3 Hz, 1H, C*H*OH), 2.19 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ: 207.1, 160.5, 136.5, 128.9, 115.7, 95.6, 73.4, 18.4. IR spectra (KBr, cm^{-1}): 3459, 1716, 1511, 1450, 1384, 1097, 1307, 1097, 758, 669. HPLC (Chiralcel AD, *n*-hexane/*i*-PrOH=9/1, flow rate=1.0 mL/min, λ=254 nm, t_1 (minor)=11.2 min, t_2 (major)=12.7 min). Elemental analysis calcd for $C_{10}H_{11}FO_3$: C, 60.60; H, 5.59; found C, 60.84; H, 5.71.

*4.3.2. 4-((1S,2R)-1,2-dihydroxy-3-oxobutyl)benzaldehyde (**9f**).* Colorless oil; $[\alpha]_D^{20}$ +32.4 (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ: 10.03 (s, 1H, C*H*O), 7.92 (d, *J*=8.0 Hz, 2H, Ar), 7.61 (d, *J*=8.0 Hz, 2H, Ar), 5.17 (d, *J*=2.5 Hz, 1H, C*H*OH), 4.41 (d, *J*=2.7 Hz, 1H C*H*OH), 2.17 (s, 1H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 208.5, 191.9, 148.9, 135.1, 129.4–126.5 (Ar), 80.4, 79.4, 73.1, 67.8, 25.9. IR spectra (KBr, cm^{-1}): 3460, 1703, 1609, 1419, 1360, 1307, 1064, 844, 668. HPLC (Chiralcel

AD, *n*-hexane/*i*-PrOH=9/1, flow rate=1.0 mL/min, λ=254 nm, t_1 (minor)=15.5 min, t_2(major)=16.7 min). Elemental analysis calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; found C, 63.31; H, 5.89.

*4.3.3. (3R,4S)-3,4-Dihydroxy-4-(3-phenoxyphenyl)butan-2-one (**9h**).* Colorlessoil;$[\alpha]_D^{20}$+23.1(*c*1,MeOH);^{1}HNMR($CDCl_3$)δ:7.22–6.25 (9H,Ar),4.86(d,*J*=3.2Hz,1H,C*H*OH),4.50(d,*J*=3.1Hz,1H,C*H*OH),2.08(s,3H, CH_3)ppm;^{13}CNMR($CDCl_3$)δ:207.1,156.1,155.3,140.5,128.2,128.4,121.6, 120.4,117.3,116.1,95.5,73.5,18.4.IRspectra(KBr,cm^{-1}):3465,1706,1489, 1359,1250,1085,756,694.HPLC(ChiralcelAD,*n*-hexane/*i*-PrOH=9/1, flow rate=1.0 mL/min, λ=254 nm, t_1 (minor)=15.1 min, t_2(major)= 18.4min).ElementalanalysiscalcdforC$_{16}$H$_{16}$O$_4$:C,70.57;H,5.92;foundC, 70.73;H,6.07.

*4.3.4. (3R,4S)-3,4-Dihydroxy-4-(naphthalen-2-yl)butan-2-one (**9i**).* Colorless oil; $[\alpha]_D^{20}$ +32.7 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.88 (m, 4H, Ar), 7.51 (m, 4H, Ar), 5.20 (d, *J*=3.3 Hz, 1H, C*H*OH), 4.49 (d, *J*=3.3 Hz, 1H, C*H*OH), 2.18 (s, 1H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 207.1, 133.5–127.2 (Ar), 93.0, 75.6, 19.2. IR spectra (KBr, cm^{-1}): 3429, 1715, 1384, 1360, 1171, 1056, 758, 669. HPLC (Chiralcel AD, *n*-hexane/*i*-PrOH=7/3, flow rate=0.7 mL/min, λ=254 nm, t_1(minor)=7.3 min, t_2(major)=10.2 min). Elemental analysis calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; found C, 73.28; H, 6.26.

*4.3.5. (3R,4S)-3,4-Dihydroxy-4-(thiophen-2-yl)butan-2-one (**9j**).* Pale-yellow oil; $[\alpha]_D^{20}$ +42.4 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, 1H, Ar), 7.13 (m, 1H, Ar), 6.98 (m, 1H, Ar), 5.28 (d, *J*=2.75 Hz, 1H, *CH*OH), 4.42 (d, *J*=2.75 Hz, 1H, CH, *CH*OH), 2.25 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 207.5, 205.3, 143.6, 127.1–124.7 (Ar), 80.8, 70.8, 69.0, 29.8, 25.3. IR spectra (KBr, cm^{-1}): 3460, 1711, 1531, 1359, 1230, 1160, 1063, 750, 685. HPLC (Chiralcel AD, *n*-hexane/*i*-PrOH=9/1, flow rate=1.0 mL/min, λ=254 nm, t_1(minor)=7.7 min, t_2(major)=8.1 min). Elemental analysis calcd for $C_8H_{10}O_3S$: C, 51.60; H, 5.41; found C, 51.49; H, 5.52.

*4.3.6. (3R,4S)-4-Hydroxy-3-methoxy-4-thiophen-2-yl-butan-2-one (**9m**).* Pale-yellow oil; $[\alpha]_D^{20}$ +38.4 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.31(m, 1H, Ar), 7.05 (m, 1H, Ar), 6.99 (m, 1H, Ar), 5.17 (d, *J*=3.3 Hz, 1H, C*H*OH), 3.81 (d, *J*=3.3 Hz, 1H, C*H*OH), 3.49 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 207.3, 146.3, 126.3, 125.5, 124.5, 102.4, 80.0, 51.5, 19.2. IR spectra (KBr, cm^{-1}): 3462, 1704, 1529, 1360, 1223, 1165, 1060, 755, 690. HPLC (Chiralcel AD, *n*-hexane/*i*-PrOH 7/3, flow rate=0.7 mL/min, λ=254 nm, t_1(minor)=10.4 min, t_2(major)= 13.8 min). Elemental analysis calcd for $C_9H_{12}O_3S$: C, 53.98, H, 6.04; found C, 54.16, H, 5.95.

4.4. Catalyst recycling

Fresh portions of starting compounds **7a** and **8a**, toluene and AcOH if specified were added to the catalyst **1a**, that remained after the extraction of the product **9a**, and the reaction was *re*-performed as described in the procedure 4.3 (Table 3).

4.5. Synthesis of (1*S*,2*R*,3*R*)-1-(2-nitrophenyl)butane-1,2,3-triol (10)

Sodium borohydride (63.4 mg, 1.67 mmol) was added to a solution of 3,4-dihydroxy-4-(2-nitrophenyl)-butane-2-one (**9b**) (37 mg, 0.17 mmol) in MeOH (1.5 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 30 min, diluted with water (1.5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo (20 Torr), the residue was purified by column chromatography on silica gel (0.060–0.200 nm, eluent EtOAc/*n*-hexane 1:1) to afford the compound **10** (33 mg, 80%) as colorless oil.[8a]

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.017.

References and notes

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