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A new (*S*)-prolinamide modified by an ionic liquid moiety—a high performance recoverable catalyst for asymmetric aldol reactions in aqueous media

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ABSTRACT

New prolinamide derivatives modified with ionic liquid moieties were synthesized and studied as organocatalysts in asymmetric aldol reactions in water. Aldol reactions between cycloalkanones or methylketones and aromatic aldehydes proceeded under studied conditions with high conversions (yields), diastereo- and enantioselectivities in the presence of a hydrophobic catalyst bearing a PF_6 anion (1–5 mol %). The procedure is scalable and the catalyst retained its diastereo- and enantioselectivity over at least four reaction cycles and its activity over at least three reaction cycles.

1. Introduction

Asymmetric organocatalysis is an intensively developing area of modern organic chemistry.[1] α-Aminoacid, imidazolidin-4-one or cinchona derivatives as well as some other small chiral molecules used as catalysts allow the synthesis of complex polyfunctional compounds of high enantiomeric purity from simple achiral precursors.[2] The asymmetric aldol reaction is one of the most important organocatalytic reactions and an irreplaceable instrument in organic chemists and Nature's toolboxes for forming a C–C bond in organic compounds, in particular in saccharides.[3] In living systems, aldol reactions are catalyzed by aldolases, which have a peptide structure.[4] In the laboratory, these are normally performed in the presence of α-aminoacids (proline first of all)[5] and their derivatives.[6] Lower peptides[7] and proline amides bearing a β-aminoalcohol moiety[8] are among the most active and enantioselective organocatalysts.

Apart from the structural similarity, there are some differences in the behaviour of aldolases and organocatalysts. As a rule, reactions in the presence of organocatalysts are performed in organic solvents or under solvent-free conditions[9a–d] whereas enzymatic reactions are run in an aqueous environment. Another distinction is that aldolases retain their extremely high catalytic activity in thousands of catalytic cycles whereas the majority of organocatalysts are 'washed out' during the reaction workup and their regeneration is challenging.[9e]

Recently, some organocatalysts that repeatedly catalyze aldol reactions in aqueous media and can be regenerated have been synthesized. Normally, these organocatalysts contain an α-aminoacid moiety linked to a polymer group (polystyrene)[10] or to an ionic fragment comprising an organic cation and hydrophobic fluorinated anion (PF_6, NTf_2).[11] The polymeric or specific ionic group presence makes it possible to recover catalysts due to their low solubility in organic solvents and water. Furthermore, they create the hydrophobic environment of the enamine-type transition state, which resembles a hydrophobic pocket of aldolases,[10e], which is essential for efficient reaction stereocontrol.

Most of recoverable proline derivatives prepared so far contain a free carboxylic group. Only a few immobilized prolinamide derivatives have been reported to be capable of catalyzing the aldol reaction in an aqueous medium, in particular compounds **1**,[12a] **2**[12b,c] and **3**[12d] (Fig. 1). However, to attain high catalytic performance poorly water-soluble polymer-supported catalysts **1** and **2** should be used in water/organic solvent mixtures (THF or $CHCl_3$). The organic additive is needed for partial dissolution or swelling of polymeric molecules. The synthesis of dendritic catalyst **3** is rather tedious.

It might be expected that recovery of prolinamide catalysts, which retain their activity and selectivity in an aqueous medium might be achieved by an ionic liquid (IL) tag insertion in the catalyst

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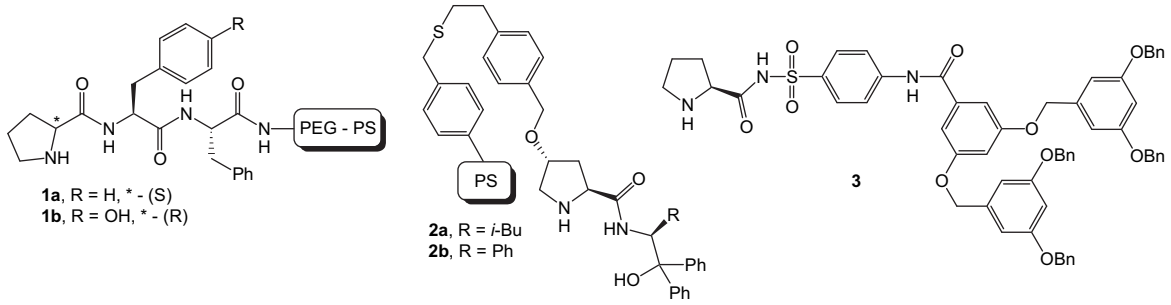


Figure 1. Prolinamide catalysts, immobilized on polymers or by a dendritic group.

structure. This combination may allow tuning the catalyst hydrophobic/hydrophilic properties to attain maximum catalytic efficiency in an aqueous environment.

2. Results and discussion

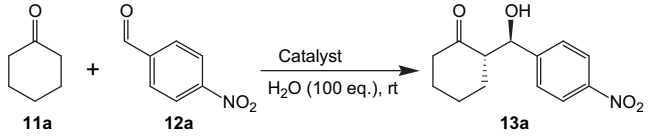
To verify this hypothesis we synthesized new IL-immobilized chiral catalysts **9** and **10**, bearing a (*S*)-diphenylvalinol (**4**) fragment. The respective prolinamide efficiently catalyzes the aldol reaction both in organic solvents[8b] and in water,[13] presumably due to a strong coordination between the catalyst NH– and OH–groups and the aldehyde acceptor in the transition state, which minimizes the unfavourable impact of hydrogen bonding between aldehyde and water molecules in the aqueous environment. As far as we know, IL-tagged prolinamide derivatives bearing more that one chiral centre have not been reported so far.

Cbz-protected 4-hydroxy-(*S*)-proline (**5**) was transformed to amide **6** by a reaction with (*S*)-diphenylvalinol (**4**) in the presence of $Et_3N/ClCO_2Et$. Alkylation of amide **6** by bromovaleric acid in the presence of the DCC/DMAP system afforded bromoester **7** The latter was converted to imidazolium salt **8** by a reaction with methylimidazole. The deprotection of bromide **8** followed by the anion exchange in amide **9** yielded hexafluorophosphate **10** (Scheme 1).

Compounds **9** and **10** have mps 103–105 and 98–100 °C, respectively and therefore can be considered as chiral ionic liquids.[14] Their solubility in water depended on the anion. Bromide **9** produced a clear 7% aqueous solution at room temperature whereas the hexafluorophosphate **10**/H_2O mixture was a suspension under the same conditions.

At first we studied compounds **9** and **10** in a model reaction between cyclohexanone (**11a**) and 4-nitrobenzaldehyde (**12a**) in an aqueous medium (Table 1). The reactions were run in a large water excess (100 equiv relative to aldehyde) at 3–25 °C. The ketone/aldehyde ratio was 3/1.

Table 1
Activity and selectivity of catalysts **9**, **10** in the model reaction

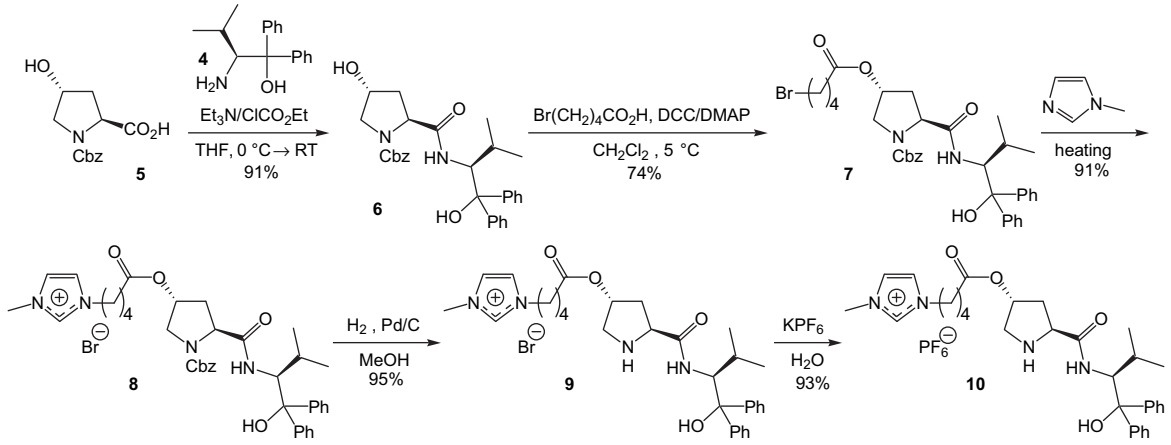


Entry	Catalyst (mol %)	t, h	Conv., %	*dr* (*anti*/*syn*)	*ee* (*anti*), %
1	**10** (10)	4	>99	88/12	84
2	**10** (5)	4.5	>99	94/6	89
3	**10** (1)	4.5	>99	97/3	97
4[a]	**10** (1)	8	99 (97)[b]	96/4	98
5[c]	**10** (1)	18	98	99/1	99
6[d]	**9** (5)	15	>99	81/19	81
7	**9** (5)	20	>99	85/15	89

[a] Scaling: 7 mmol of aldehyde was used.
[b] Isolated yield in brackets.
[c] The reaction was run at +3 °C.
[d] 25 equiv of water was used.

In the presence of both catalysts the reaction proceeded with a high conversion yielding aldol **13a**. Its rate and selectivity were higher in the presence of hydrophobic catalyst **10** than under the action of hydrophilic catalyst **9**. For that, the very fact of the available pronounced catalytic activity of water-soluble amide **9** differentiates prolinamide-type catalysts from their respective hydrophilic amino acids derivatives bearing free carboxylic group that did not catalyze aldol reactions in aqueous solutions.[11a,c]

The reaction diastereo- and enantioselectivity increased with reduction of the loading of compound **10** and a lower reaction



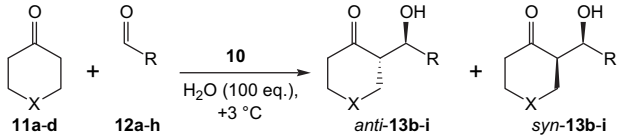
Scheme 1. Synthesis of prolinamide derivatives **9** and **10** bearing IL moieties.

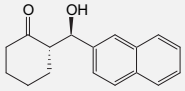
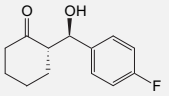
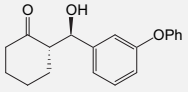
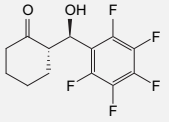
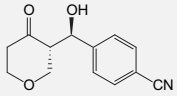
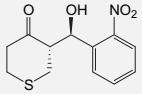
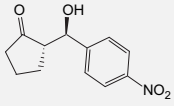
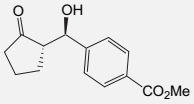
temperature. The best results were attained in the presence of 1 mol % of **10** at 3 °C. A lower loading is another advantage of prolinamide-type catalysts as compared with modified α-amino-acids with free carboxylic group, which should be taken in amounts as high as 10–15 mol % to attain high process efficacy. The procedure is scalable: yield as well as diastereo- and enantiomeric excess of product **13a** remained the same when the reaction was run on a 7 mmol scale. Furthermore, the scaling-up procedure makes the reaction more attractive from green-chemistry point of view because it allows a significantly reduced amount of organic solvent (Et_2O) for product isolation (see Experimental section).

Next, we examined catalyst **10** in aldol reactions between cycloalkanones **11a–d** and aromatic aldehydes **12a–h** (Table 2). **12d** (R=3–PhO–C_6H_4) was less active under the studied conditions: as high as 5 mol % of catalyst **10** should be added to achieve high conversion. Cyclopentanone (**11d**) reacted with aromatic aldehydes yielding mixtures of *anti*- and *syn*-diastereomers of the corresponding aldols **13h,i** in similar amounts. *Ee*s of major *anti*-isomers were close to that obtained for six-membered cycloalkanones **11a–c**. As a rule, conversions, diastereo- and enantioselectivities of aldol reactions, catalyzed by compound **10**, were comparable to those reported for other organocatalysts bearing a prolinamide unit.

Furthermore, unlike IL-modified proline derivatives with a free carboxylic group,[11] prolinamide **10** catalyzed reactions of aromatic aldehydes with methylketones **14a–e**, in particular those contain-

Table 2
Aldol reactions between cycloalkanones **11a–d** and aromatic aldehydes **12a–h** in the presence of **10**

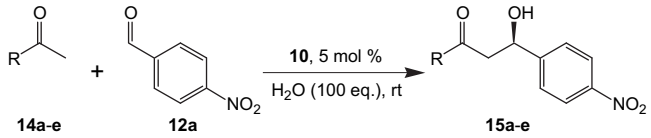


Entry	11,12	Aldol	13	10 (mol %)	t, h[a]	Conv.,[a] %	*dr* (*anti*/*syn*)[a]	*ee* (*anti*),[a] %
1	**11a**, **12b**		**b**	2	36 (48[15a])	>95 (23[15a])	98/2 (95/5[15a])	99 (68–83[15a])
2	**11a**, **12c**		**c**	2	40 (72[12d])	69/64[b] (85[b,12d])	97/3 (98/2[12d])	99 (95[12d])
3	**11a**, **12d**		**d**	5	45 (90[11c])	77/71[b] (87[11c])	96/4 (96/4[11c])	94 (>99[11c])
4	**11a**, **12e**		**e**	1	15 (16[15a])	>99/97[b] (86[15a])	99/1 (95/5[15a])	99 (97[15a])
5	**11b**, **12f**		**f**	2	48 (nd[15b])	97 (81[b,15b])	99/1 (97/3[15b])	97 (99[15b])
6	**11c**, **12g**		**g**	2	48 (nd[15b])	88 (93[b,15b])	93/7 (98/2[15b])	92 (99[15b])
7 8[d]	**11d**, **12a**		**h**	2	16 16 (18[12d])	88 12 (96[12d])	62/38 44/56 (79/21[12d])	94; 9[c] 88; 57[c] (98[12d])
9	**11d**, **12h**		**i**	2	16	>99	64/36	97; 32[c]

[a] Reported data for other catalysts are given in brackets.
[b] Isolated yield.
[c] *Ee* of *syn*–aldol.
[d] Reaction under neat conditions.

The corresponding aldols **13b–i** were obtained in all cases, although the required catalyst feed depended on the reagent's structure. Reactions of cycloalkanones **11a–d** with 2-naphthylbenzaldehyde (**12b**) and aromatic aldehydes **12a**,**c**,**e–i** bearing electron-withdrawing groups (F, CN, NO_2, CO_2Me, entries 1,2,4–9) proceeded in the presence of 1–2 mol % of catalyst **10**. Aldehyde bearing alkyl, alkenyl, benzyl or cyclopropyl groups. The reactions ran regioselectively at the methyl group of ketones **14a–e** under the studied conditions affording chiral aldols **15a–e** (Table 3) in moderate to high yields. The enantioselectivities of these reactions were comparable to those obtained under the action of most efficient reported organocatalysts.

Table 3
Aldol reactions between methylketones **14a–e** and 4-nitrobezaldehyde (**12a**) in the presence of **10**



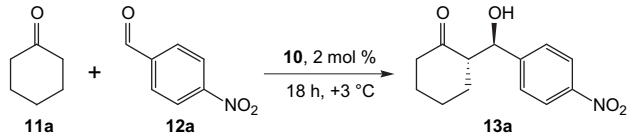
14a-e 12a 15a-e

Entry	R	14,15	t, h[a]	Yield,[a] %	*ee*,[a] %
1	cyclopropyl	**a**	47	48	97
2[b]			47	38	82
			(50[15c])	(54[15c])	(45[15c])
3	*n*-propyl	**b**	38	95	82
4[b]			38	92	75
			(35[15d])	(75[15d])	(85[15d])
5	*n*-hexyl	**c**	25	94	86
			(24[15d])	(80[15d])	(85[15d])
6	$Me_2C{=}CH(CH_2)_2$-	**d**	72	65	89
			(60[15c])	(38[15c])	(52[15c])
7	Bn	**e**	40	77	91

[a] Reported data for other catalysts are given in brackets.
[b] Reaction under neat conditions.

The recoverability of catalyst **10** was examined in the reaction between cyclohexanone (**11a**) and 4-nitrobenzaldehyde (**12a**). After the reaction completion, aldol **13a** was extracted with Et_2O and replaced with fresh portions of reagents. Catalyst **10** retained its activity and selectivity over three reaction cycles. In the fourth cycle, conversion dropped to 72% but *dr* and *ee* of the product **13a** remained at the same level (Table 4).

Table 4
Multiple use of catalyst **10**



11a 12a 13a

Run	Conv., %	*dr* (*anti*/*syn*)	*ee* (*anti*), %
1	98	99/1	99
2	97	99/1	99
3	95	>99/1	99
4	72	>99/1	>99

The studied reactions were carried out in a heterogeneous organic phase (reagent phase)/water systems. Presumably, ionic catalysts **9** and **10** are partly located in the interfacial region where the catalytic transformation occurs. The concentration of the catalyst **10**, which is poorly soluble both in water and in organic phases within the reaction area should be higher than of the catalyst **9**, which explains its better catalytic performance. Water plays an important role being unclear so far: a noticeable *dr* and *ee* decrease in aldols **15a**,**b** obtained from methylketones **14a**,**b** in the presence of **10** was recorded under the water-free conditions (Table 3, entries 1–4). The aqueous phase impact was even more sizable in the reaction of 4-nitrobenzaldehyde (**12a**) with cyclopentanone (**11d**), which proceeded under neat conditions with extremely low conversion (12%) and inversion of diastereoselectivity (Table 2, entries 7, 8).

3. Conclusion

In summary, new hydrophilic and hydrophobic chiral ionic liquids bearing a prolinamide motif have been synthesized and studied as organocatalysts in asymmetric aldol reaction between unmodified ketones and aldehydes. In the presence of a hydrophobic organocatalyst, cyclic ketones and methylketones react with aromatic aldehydes in the aqueous medium affording respective aldols in high yields and with excellent regio-, diastereo- and enantioselectivities. The prepared IL-immobilized catalyst is superior to IL-immobilized proline derivatives having a free carboxylic group in the activity and catalytic scope in the aqueous environment. It can be used in the aldol reaction four times and display the same selectivity and slightly lowered activity.

4. Experimental section

4.1. Typical procedure for the aldol reaction

A mixture of the appropriate organocatalyst (1–10 μmol), ketone **11**/**14** (0.30 mmol), aldehyde **12** (0.1 mmol), and distilled water (0.045–0.18 mL) (for reactions in aqueous media) was stirred at mentioned temperature for the period given in Tables 1–4. Aldol **13**/**15** and remained starting compounds were extracted with Et_2O (2×3 mL), combined extracts were filtered through a silica gel pad (1 g) and evaporated in vacuo (15 Torr). In case of reusing of the catalyst **10**, new portions of reagents were added to remaining suspension of **10** in water and the process ran again. Conversion and *dr* values of aldols **13a–i** were measured by ^1H NMR spectroscopy. Aldols **13c**, **15a–e** were isolated by column chromatography (silica gel Acros, 0.035–0.070 mm, 60A, eluent: *n*-hexane/EtOAc=4/1). *Ee* values of **13** and **15** were determined by HPLC, chiral phase: Chiralcel OD-H, OJ-H, Chiralpak AD-H. NMR spectra and HPLC data for aldols **13** and **15** are available in articles, cited in Tables 2 and 3.

4.2. Scaling-up procedure for the aldol reaction

A mixture of catalyst **10** (47.5 mg, 0.07 mmol), cyclohexanone (**11a**, 2.15 mL, 21 mmol), 4-nitrobenzaldehyde (**12a**, 1.06 g, 7 mmol), and distilled water (6.3 mL, 0.35 mol) was stirred at room temperature for 8 h. Aldol **13a** and excess of cyclohexanone (**11a**) were extracted with Et_2O (2×3 mL). Combined extracts were evaporated in vacuo (15 Torr). The product was isolated by column chromatography on silica gel (Acros, 0.035–0.070 mm, 60A, eluent: *n*-hexane/EtOAc=3/1) and dried in vacuo (0.5 Torr) for 30 min to afford **13a** (1.7 g, 97%), light-yellow solid, mp 99–100 °C.

4.3. Benzyl (4*R*)-hydroxy-(2*S*)-((1*S*)-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl)-pyrrolidine-1-carboxylate 6

A solution of ethyl chloroformate (0.34 mL, 3.50 mmol) in THF (10 mL) was added dropwise during 10 min to a stirred mixture of

Cbz-protected 4-hydroxy-(*S*)-proline (0.93 g, 3.50 mmol) and Et_3N (0.49 g, 3.50 mmol) in THF (20 mL) at 0–5 °C. After 20 min a solution of (*S*)-diphenylvalinole (0.89 g, 3.50 mmol) in THF (10 mL) was added dropwise during 10 min. The resulting mixture was stirred for 2 h at 0–5 °C and for 1 h at ambient temperature, then it was filtrated off and washed with THF (15 mL). The combined organic extracts were evaporated, and the residue was washed with Et_2O (2×10 mL) to afford **6** (1.60 g, 91%) as white solid, mp 219–221 °C; $[\alpha]_D^{23}$ −59.9 (*c* 0.67, *i*-PrOH); ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.61 (4H, d, J=7.7 Hz, $2H^2H^6$(Ph)), 7.09–7.43 (11H, m, $2H^{3-5}$(Ph), C_6H_5(Cbz)), 5.10–5.29 (2H, m, CH_2Ph), 4.88–4.98 (1H, m, *CH*NHCO), 4.16–4.36 (2H, m, *CH*O, *CH*CONH), 3.39–3.55 (2H, m, CH_2N), 1.61–2.01 (2H, m, CH_2CHN), 1.25–1.58 (1H, m, $CH(CH_3)_2$), 0.70–1.07 (6H, m, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 171.6, 154.0, 147.4, 146.0, 136.9, 128.2, 127.9, 127.4, 126.0, 125.8, 125.0, 81.1, 68.4, 65.7, 59.0, 57.8, 55.3, 37.7, 28.0, 22.7, 18.0; IR (KBr, cm^{-1}): 3364, 3292, 2956, 2944, 2872, 1660, 1524, 1432, 1352, 1304, 1180, 1124, 1156, 968, 912; Elemental analysis calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57; O, 15.92; found C, 71.96; H, 6.75; N, 5.51.

4.4. Benzyl (4*R*)-(5-Bromo-pentanoyloxy)-(2*S*)-((1*S*)-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl)-pyrrolidine-1-carboxylate 7

A mixture of amide **6** (1.52 g, 3.03 mmol), 5-bromovaleric acid (0.56 g, 3.09 mmol), DCC (0.63 g, 3.06 mmol) and DMAP (0.025 g, 0.20 mmol) in CH_2Cl_2 (20 mL) was stirred at 5 °C for 8 h. The resulting precipitate was filtered off and washed with CH_2Cl_2 (3×10 mL). The combined organic extracts were evaporated, and the residue was purified by column chromatography on silica gel (Acros, 0.035–0.070 mm, 60A, eluent: *n*-hexane/EtOAc=4/1) and dried in vacuo (0.5 Torr) for 2 h to afford bromoester **7** (1.49 g, 74%) as white solid, mp 166–168 °C; $[\alpha]_D^{21}$ −59.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (4H, d, *J*=5.1 Hz, $2H^2H^6$(Ph)), 7.11–7.39 (11H, m, $2H^{3-5}$(Ph), C_6H_5(Cbz)), 5.11–5.23 (2H, m, CH_2Ph), 4.83 (1H, d, *J*=10.3 Hz, *CH*NHCO), 4.25 (1H, t, *J*=7.5 Hz, *CH*CONH), 4.07 (1H, d, *J*=7.7 Hz, *CH*O), 3.41–3.62 (2H, m, CH_2N), 3.37 (2H, t, *J*=6.4 Hz, CH_2Br), 3.17 (1H, s, O*H*), 2.26 (2H, t, *J*=7.2 Hz, CH_2CO), 1.56–2.00 (6H, m, $(CH_2)_2CH_2$Br, CH_2CHN), 1.26–1.45 (1H, m, $CH(CH_3)_2$), 0.76–0.97 (6H, m, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 172.3, 171.1, 155.4, 146.5, 145.4, 136.3, 128.5, 128.4, 128.2, 128.0, 126.8, 125.4, 81.9, 72.8, 67.4, 59.2, 59.0, 52.3, 33.9, 33.1, 32.7, 31.8, 28.8, 23.3, 22.8, 18.0; IR (KBr, cm^{-1}): 3400, 2960, 2928, 2872, 1732, 1700, 1660, 1532, 1420, 1356, 1172, 1128, 1064, 1000, 972, 920, 892; Elemental analysis calcd for $C_{35}H_{41}BrN_2O_6$: C, 63.16; H, 6.21; Br, 12.00; N, 4.21; O, 14.42; found C, 63.40; H, 6.15; Br, 12.03; N, 4.17.

4.5. Benzyl (4*R*)-(5-(1-Methyl-1*H*-imidazol-3-ium-3-yl)) pentanoyloxy)-(2*S*)-((1*S*)-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-pyrrolidine-1-carboxylate bromide 8

A mixture of **7** (1.00 g, 1.50 mmol) and 1-methylimidazole (0.30 g, 3.66 mmol) was heated at 100 °C for 20 min with continuous stirring and then cooled to ambient temperature. The resulting viscous yellow oil became white solid as washed with Et_2O (6×10 mL). The precipitate was dried in vacuo (0.5 Torr) for 2 h to afford **8** (1.02 g, 91%) as white solid, mp 131–133 °C; $[\alpha]_D^{21}$ −62.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.09 (1H, s, NC*H*N), 8.21 (1H, d, J=10.3 Hz, NCHC*H*N), 7.54–7.66 (4H, m, $2H^2H^6$(Ph)), 7.02–7.40 (12H, m, $2H^{3-5}$(Ph), C_6H_5(Cbz), NC*H*CHN), 4.92–5.27 (4H, m, CH_2Ph, *CH*NHCO, *CH*O), 4.57 (1H, t, J=8.3 Hz, *CH*CONH), 4.31–4.40 (2H, m, CH_2CH_2N), 3.96 (3H, s, CH_3N), 3.56–3.79 (2H, m, $CHCH_2$N), 2.24–2.42 (2H, m, CH_2CO), 1.49–2.09 (6H, m, $(CH_2)_2CH_2$N, CH_2CHN), 1.30–1.45 (1H, m, $CH(CH_3)_2$), 0.69–1.14 (6H, m, $(CH_3)_2$CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 171.9, 171.6, 154.6, 147.4, 145.7, 136.7, 128.3, 127.9, 127.5, 126.1, 125.6, 125.2, 123.2, 122.2, 120.3, 81.9, 73.2, 66.8, 59.0, 58.8, 52.6, 49.3, 36.3, 35.2, 33.3, 29.3, 28.4, 22.8, 21.2, 18.6; IR (KBr, cm^{-1}): 3350, 3148, 3064, 2956, 2872, 1732, 1704, 1560, 1448, 1420, 1356, 1168, 1120, 1064, 1004, 912; Elemental analysis calcd for $C_{39}H_{47}BrN_4O_6$: C, 62.65; H, 6.34; Br, 10.69; N, 7.49; O, 12.84; found C, 62.83; H, 6.22; Br, 10.60; N, 7.54.

4.6. (4*R*)-(5-(1-Methyl-1*H*-imidazol-3-ium-3-yl)) pentanoyloxy)-(2*S*)-((1*S*)-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-pyrrolidine bromide 9

A mixture of **8** (0.90 g, 1.20 mmol) and Pd/C (5%, 0.09 g) in dry CH_3OH (25 mL) was stirred under H_2 (760 Torr) at ambient temperature for 3 h. The resulting precipitate was filtered off and washed with CH_3OH (10 mL). The combined organic phases were evaporated, and the residue was dried in vacuo (0.5 Torr) for 2 h to afford **9** (0.70 g, 95%) as white solid, mp 103–105 °C; $[\alpha]_D^{22}$ −40.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.49 (1H, s, NC*H*N), 8.27 (1H, d, J=10.3 Hz, NCHC*H*N), 7.57 (4H, d, *J*=7.3 Hz, $2H^2H^6$(Ph)), 7.06–7.37 (7H, m, $2H^{3-5}$(Ph), NC*H*CHN), 5.05–5.11 (1H, m, *CH*O), 4.77 (1H, dd, J_1=9.5 Hz, J_2=2.6 Hz, *CH*NHCO), 4.37 (2H, t, *J*=7.3 Hz, NCH_2CH_2), 4.05 (3H, s, NCH_3), 3.88 (2H, t, *J*=8.4 Hz, *CH*CONH), 3.05 (1H, d, *J*=12.8 Hz, CHC*H*HN), 2.91 (1H, dd, J_1=13.0 Hz, J_2=3.8 Hz, CHCH*H*N), 2.37 (2H, t, *J*=7.0 Hz, CH_2CO), 1.89–2.52 (2H, m, CH_2CHN), 1.88–2.05 (2H, m, CH_2CH_2N), 1.60–1.74 (2H, m, CH_2CH_2CO), 1.25–1.49 (1H, m, $CH(CH_3)_2$), 0.98 (3H, d, *J*=6.6 Hz, $CHCH_3$), 0.81 (3H, d, *J*=7.0 Hz, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 173.4, 172.1, 147.2, 145.6, 136.8, 128.9, 127.9, 127.7, 126.2, 125.6, 125.3, 123.3, 122.3, 81.5, 75.9, 59.6, 52.5, 49.3, 36.4, 33.2, 29.2, 28.5, 24.7, 22.8, 21.0, 18.5; IR (KBr, cm^{-1}): 3384, 3148, 2956, 2872, 1728, 1660, 1564, 1524, 1448, 1368, 1250, 1168, 1064, 1032; Elemental analysis calcd for $C_{31}H_{41}BrN_4O_4$: C, 60.68; H, 6.74; Br, 13.02; N, 9.13; O, 10.43; found C, 60.89; H, 6.68; Br, 13.00; N, 9.14.

4.7. (4*R*)-(5-(1-Methyl-1*H*-imidazol-3-ium-3-yl)) pentanoyloxy)-(2*S*)-((1*S*)-(hydroxy-diphenyl-methyl)-2-methyl-propylcarbamoyl]-pyrrolidine hexafluorophosphate 10

A solution of KPF_6 (0.10 g, 0.54 mmol) in water (5 mL) was added to a solution of **9** (0.30 g, 0.49 mmol) in water (10 mL). The resulting precipitate washed with distilled water (2×5 mL) and dried in vacuo (0.5 Torr) for 2 h to afford **10** (0.31 g, 93%) as while solid, mp 98–100 °C; $[\alpha]_D^{22}$ −30.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.46 (1H, s, NC*H*N), 7.98 (1H, d, *J*=9.5 Hz, NCHC*H*N), 7.53 (4H, t, *J*=8.2 Hz, $2H^2H^6$(Ph)), 7.06–7.38 (7H, m, $2H^{3-5}$(Ph), NC*H*CHN), 5.01–5.08 (1H, m, *CH*O), 4.69 (1H, d, *J*=8.1 Hz, *CH*NHCO), 4.11 (2H, t, *J*=7.3 Hz, NCH_2CH_2), 3.82 (3H, s, NCH_3), 3.78 (2H, t, *J*=7.7 Hz, *CH*CONH), 3.05 (1H, d, *J*=12.5 Hz, CHC*H*HN), 2.76 (1H, d, *J*=11.8 Hz, CHCH*H*N), 2.30 (2H, t, *J*=5.9 Hz, CH_2CO), 1.95–2.38 (2H, m, CH_2CHN), 1.79–1.92 (2H, m, CH_2CH_2N), 1.49–1.64 (3H, m, CH_2CH_2CO, $CH(CH_3)_2$), 0.93 (3H, d, *J*=6.2 Hz, $CHCH_3$), 0.83 (3H, d, *J*=6.6 Hz, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 173.8, 172.2, 146.6, 145.2, 127.8, 127.5, 126.2, 125.2, 125.0, 123.1, 121.7, 81.0, 75.7, 59.3, 52.3, 48.9, 36.4, 35.5, 32.6, 28.4, 28.3, 22.5, 20.5, 17.9; IR (KBr, cm^{-1}): 3370, 3148, 2956, 2872, 1730, 1664, 1564, 1524, 1448, 1368, 1252, 1168, 1064, 1032; Elemental analysis calcd for $C_{31}H_{41}F_6N_4O_4P$: C, 54.86; H, 6.09; F, 16.80; N, 8.26; O, 9.43; P, 4.56; found C, 55.01; H, 6.03; F, 1659; N, 8.22.

4.8. 4-Hydroxy-4-(4-nitrophenyl)-1-phenylbutan-2-one 15e

Ee: 91%; mp 92–94 °C; $[\alpha]_D^{21}$ 36.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (2H, d, J=8.4 Hz, H^3H^5(4-NO_2-Ph)), 7.46 (2H, d, *J*=8.8 Hz, H^2H^6(4-NO_2-Ph)), 7.11–7.39 (5H, m, C_6H_5), 5.22 (1H, t, *J*=5.7 Hz, *CH*OH), 3.74 (2H, s, PhCH_2), 3.54 (1H, br, O*H*), 2.87 (2H, d, *J*=4.7 Hz, CH_2CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.1, 150.1, 147.2, 133.1, 129.4, 128.9, 127.4, 126.4, 123.6, 69.0, 50.7, 49.8; IR (KBr, cm^{-1}): 3464, 1708, 1604, 1512, 1348, 1080, 1060, 852, 824; R_f=0.66 (*n*-hexane/EtOAc=2/1); HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH=7/3,

flow rate=0.8 mL/min, λ=254 nm, t_1 (major)=30.3 min, t_2 (minor)=32.2 min); Elemental analysis calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91; O, 22.43; found C, 67.61; H, 5.19; N, 4.94.

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