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Note

D-Glucosamine in a chimeric prolinamide organocatalyst for direct asymmetric aldol addition

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ABSTRACT

O-TBDPS D-glucosamine coupled with L-proline is reported to act as an efficient organocatalyst in the accomplishment of direct aldol reactions. Excellent results, in terms of chemical yields, as well as diastereomeric and enantiomeric ratios, are reported for the catalyzed additions of cyclohexanone and acetone to variously substituted benzaldehydes.

L-Proline, among the simple natural molecules from the 'chiral pool', is well recognized to function as an asymmetric organocatalyst leading to appreciable levels of enantioselectivity in a range of synthetic transformations.[1] Most importantly, it works like an enzyme mimic of the class I aldolase,[2] catalyzing an important organic asymmetric transformation, the aldol reaction.[3,4]

However, the simple proline molecule has not been demonstrated to be an efficient catalyst in aqueous medium,[2(e),5] likely due to the fact that water itself alters enantioselectivities[6] by interrupting the hydrogen bonds that are crucial for stabilizing the transition states of the asymmetric catalytic reactions.[7] Either the use of cosolvents or, vice versa, attempts to enhance the hydrophilic nature of proline by grafting on it polyhydroxylated auxiliaries,[8] did not lead to significantly improved results.

Indeed, having in mind the catalytic mechanism of proline, another non secondary aspect is that the reactions occurring in the aldolase antibodies are considered to be accomplished in a hydrophobic active site,[9] where the amino functionality of lysine and the hydroxyl group of tyrosine seem to be also involved in the catalytic cycle. This is corroborated by the encouraging results[1a,10] obtained when small organic molecules bearing hydrophobic groups (thus designed with the purpose of matching the hydrophobic nature of the active site in antibodies) were used to catalyze the asymmetric aldol addition.

Under such circumstances we were stimulated to design a new catalyst that, in our opinion, should have overcome the above mentioned limits of other reported proline-based catalysts. It consists of L-prolinamide **1** obtained from both commercial D-glucosamine and L-proline (as shown in Scheme 1) and displays, as highlighted in Figure 1, three different domains, namely a hydrophobic one, represented by the cumbersome TBDPS protecting group at the anomeric hydroxyl of β-glucosamine, a hydrophilic one, consisting of the sugar moiety with its three free hydroxyl groups, and finally the functional domain represented by L-proline nucleus.

Simple D-glucosamine, indeed, had been already demonstrated[11] to exert a catalytic role on direct aldol reaction of ketones and aromatic aldehydes, although affording moderate yields and poor enantiomeric excess of the aldol product. As poor, and even worse, results were reported[8b] for the use of unprotected D-glucosamine-L-prolinamide as catalyst for the same kind of reactions in water. Considering, on the other hand, that small proline-based molecules bearing hydrophobic groups,[10c] as already mentioned above, had been reported to exhibit good catalytic activity for aldol reactions, we combined all the information in the same molecule that, as expected, turned out to be an excellent organocatalyst to accomplish direct aldol reaction of cyclohexanone and aromatic aldehydes.

The new catalyst was extensively tested in the direct aldol addition of cyclohexanone to variously substituted benzaldehydes,

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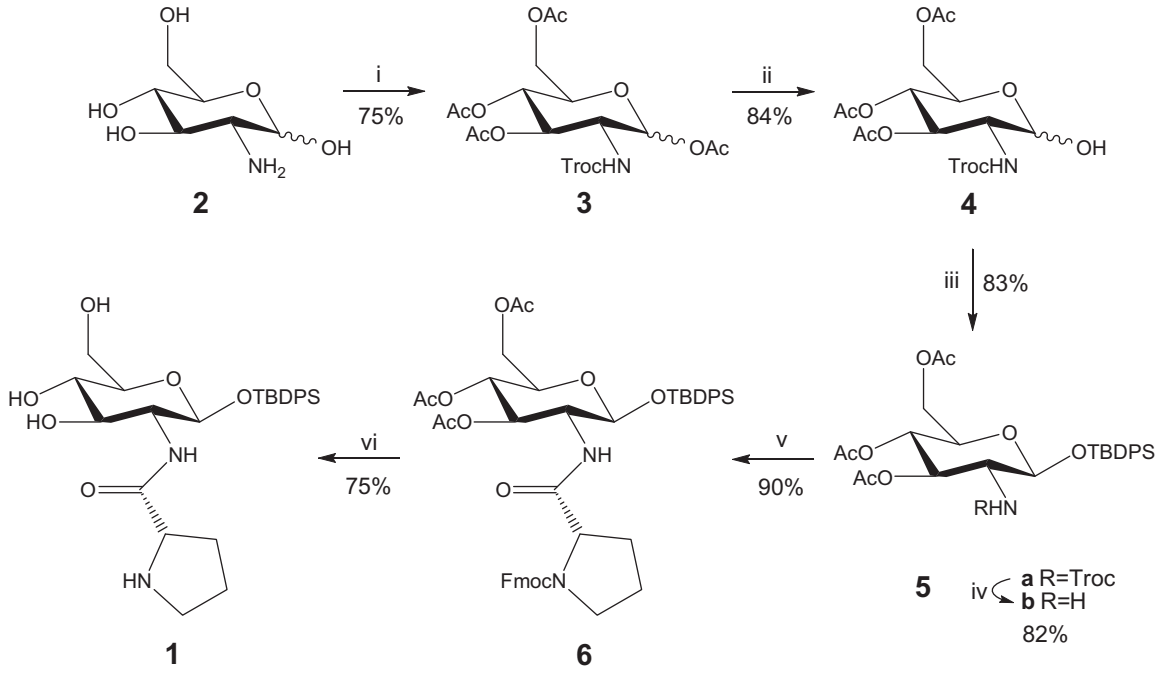


Scheme 1. Synthesis of **1** from commercial D-glucosamine and L-proline. Reagents and conditions: (i) (a) Cl_3CH_2OCOCl, $NaHCO_3$; (b) $(Ac)_2O$, Py; (ii) $BnNH_2$; (iii) (a) ImH, TBDPSiCl; (iv) Zn, glacial AcOH; (v) Fmoc-Pro-OH, HOBt, EDC; (vi) NH_3, MeOH.

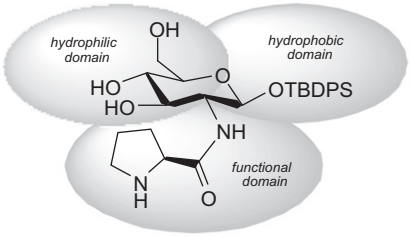


Figure 1. (2*R*)-Pyrrolidine-2-carboxamide, **1**.

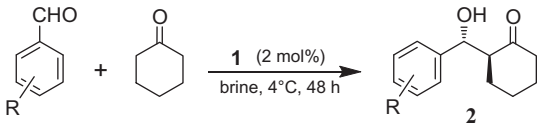
under standardized conditions (2 mol % loading in brine, 4 °C, 48 h) obtaining rather impressive results (Table 1).

Some other miscellaneous experiments, carried out using different catalyst loadings/solvents/temperatures/reaction times, are reported in Table 2.

All the results show unambiguously that **1** is an efficient catalyst working in aqueous medium (see the poor results of the reactions carried out in THF, Table 2) at low temperature. The very low catalyst loading (down to 0.1 mol %, Table 2) that can be utilized, as well as the significant catalyst recovery (72–89%) and its reuse are noteworthy (Table 3).

Compound **1** was also tested by the addition of acetone and 4-nitrobenzaldehyde (Table 4). The reaction with acetone was carried out both in the presence and in the absence of water. In the first case (entries 1–3) the aldol product was obtained in rather acceptable yields (42–54%), significantly higher than the yields (10–12%) obtained in THF (entries 4 and 5). The enantioselectivities in both cases were substantially similar. In our opinion the aromatic aldehyde, that is scarcely soluble in hydrophilic medium (brine), tends to position itself in the hydrophobic pocket of the catalyst, thus being more available for the enamine nucleophilic attack. Otherwise, in the absence of water (THF), acetone and aromatic aldehyde are both well dissolved in the organic solvent and this may cause a slower reaction. No reversed configuration of the aldol product was observed.[12] Our results, however, are

Table 1
Cyclohexanone/miscellaneous benzaldehydes aldol additions in brine, 4 °C, 48 h, catalyzed by **1** (2 mol %)



R	Yield[a] (%)	dr (*anti:syn*)[b]	ee[c] (%)
3-Chloro	99	96:4	96
4-Chloro	99	97:3	98
3-Cyano	86	98:2	96
4-Cyano	>99	97:3	96
3-Fluoro	98	96:4	96
4-Fluoro	99	96:4	98
2-Methoxyl	95	88:12	83
3-Methoxyl	>99	92:8	94
4-Methoxyl	96	87:13	82
3-Methyl	99	95:5	94
4-Methyl	98	92:8	87
2-Nitro	96	98:2	>99
3-Nitro	>99	97:3	98
4-Nitro	98	97:3	96
4-Isopropyl	98	91:9	92

[a] After chromatography.
[b] Determined by ^1H NMR.
[c] Determined by HPLC on chiral column.

mostly paralleling those reported by various authors for the aldol addition of acetone and aromatic aldehydes in the presence of water.[2e,4d,10a,12,13]

The performances of the catalyst **1** can be accounted for by considering that in water (even more in brine, due to salting-out effect[14]) catalyst's molecules may undergo molecular aggregation, much like surfactants, creating a local hydrophobic microenvironment in which reactions can take place. In other words, in the transition state the organic nonpolar reactants would be buried in the

Table 2
Aldol additions as in Table 1, catalyzed by **1**, carried out under various reaction conditions

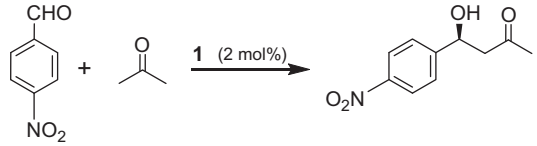
R	Mol (%)	°C	Time	Yield[a] (%)	dr (*anti*:*syn*)[b]	ee[c] (%)
4-Cyano	2	25	48 h	99	95:5	87
4-Cyano	2	−16	48 h	99	99:1	98
4-Cyano	0.1	25	4 d	92	90:10	85
4-Cyano	0.1	−16	4 d	82	99:1	99
4-Cyano (THF)	2	4	48 h	57	82:18	62
4-Nitro	10	−16	48 h	94	97:3	98
4-Nitro	2	25	48 h	98	93:7	89
4-Nitro	2	−16	48 h	96	96:4	98
4-Nitro	0.1	25	4 d	90	89:11	82
4-Nitro	0.1	−16	4 d	84	99:1	96
4-Nitro (THF)	2	4	48 h	52	90:10	70

[a] After chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC on chiral column.

Table 3
Recycle of catalyst **1**. Cyclohexanone/4-nitrobenzaldehyde aldol addition in brine, 2 mol % loading, 4 °C, 48 h.

	Yield (%)	dr (*anti*:*syn*)	ee (%)
1st run (as in Table 1)	98	97:3	96
2nd run	99	95:5	94
3rd run	82	94:6	92
4th run	66	90:10	83

Table 4
Acetone/4-nitrobenzaldehyde aldol additions, catalyzed by **1** (2 mol %), carried out under various reaction conditions



Solvent	*T* (°C)	Time	Yield[a] (%)	ee[b] (%)
Brine	25	48 h	42	66
Brine	4	48 h	54	70
Brine	−16	4 d	21	75
THF	25	48 h	10	72
THF	4	48 h	12	82

[a] After chromatography.
[b] Determined by HPLC on chiral column.

hydrophobic environment[15] whereas the entire system would be kept in water by a hydrophilic surface. After the reaction accomplishment, the moderately polar aldol molecules would be squeezed out of the hydrophobic environment and locate themselves closer to the polar surface of the catalyst.[16]

As a matter of fact, the only significant variable in the use of catalyst **1** in aqueous medium seems to be the temperature: in our opinion this is in line with the proposed transition state (Fig. 2) insofar as low temperature could reduce the molecular freedom and, consequently, contribute to the aggregation that creates a hydrophobic environment to hold the nonpolar reactants.

The results show that the synthetic catalyst **1** works 'in the presence of water'[10c,17] without organic solvent, accomplishing aldol reactions with very high enantioselectivity in most cases. It can be regarded as an interesting example of a new family of organocatalysts carrying different sugars and/or hydrophobic moieties worthy to be investigated for other C–C bond forming reactions.

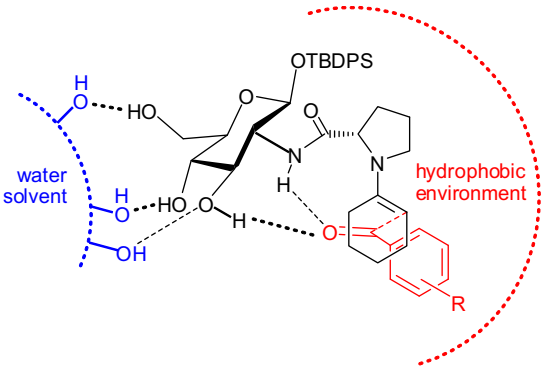


Figure 2. Proposed transition state for aldol reactions catalyzed by **1**.

1. Experimental

1.1. General

Inorganics, organic reagents, and solvents were commercial pure compounds (Aldrich, Carlo Erba) and used without further purification. TLC analyses were performed using silica gel plates (Merck, Silica Gel 60 F-254) visualized by UV light, iodine, and ninhydrin spray. Column chromatography was carried out on silica gel (Davisil 40–63 mesh).

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 500 MHz spectrometer (unless otherwise specified): chemical shifts in ppm (δ) and *J* coupling constants in Hz, solvent $CDCl_3$. The following abbreviations indicate the multiplicity: s, singlet; d, doublet; m, multiplet; br, broad signal. Chiral HPLC analyses were performed by Agilent 1100 chromatograph using Daicel ChiralPak IC column (250 × 4.6 mm) and DAD UV detector. Eluent, hexane (+TFA 0.1%)/EtOH/CH_2Cl_2 85:4:11. Flow, 1.2 mL min^{-1}. The wavelengths at which the areas of both *anti* enantiomers were read are reported in Supplementary data Table S1. Optical rotations were measured at λ = 589 nm (1.0 dm cell).

1.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α,β-D-glucopyranoside (3)[18]

To a vigorously stirred suspension of commercial D-glucosamine (4.0 g, 22 mmol) and $NaHCO_3$ (3.2 g, 38 mmol) in water (47 mL), at room temperature, trichloroethoxycarbonyl chloride (3.5 mL, 26 mmol) was added dropwise. After 2 h, the reaction mixture was treated with aq 1 M HCl until neutral and water was removed from the mixture by freeze-drying. The resulting solid residue was then diluted with pyridine (66 mL) and acetic anhydride (33 mL), the mixture being stirred overnight at room temperature. After removal of the solvents by co-evaporation with toluene under reduced pressure, the oily residue was diluted with $CHCl_3$ and aq 0.1 M HCl and shaken several times with $CHCl_3$. The combined organic extracts were washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure. Silica-gel chromatography (petr. ether/AcOEt, 1:1) of the crude product gave pure **3** (8.6 g, 16.5 mmol; yield 75%). One analytical sample: oil. Calcd for $C_{17}H_{22}Cl_3NO_{11}$ (521.03): C, 39.06; H, 4.24; N, 2.68. Found: C, 39.09; H, 4.20; N, 2.62.

^{1}H NMR: δ 2.04, 2.06, 2.10, 2.20 (s, 12H, 4 × CH_3), 3.83 (m, 1H, H-5$_\alpha$), 3.95 (m, 1H, H-2$_\beta$), 4.02 (m, 1H, H-5$_\beta$), 4.07 (m, 2H, H$_a$-6), 4.22 (m, 1H, H-2$_\alpha$), 4.28 (dd, *J* 3.8, *J* 12.3, 2H, H$_b$-6), 4.63 (d, *J* 11.8, 1H, H$_a$-Troc), 4.82 (d, *J* 11.8, 1H, H$_b$-Troc), 5.13 (br d, *J* 9.0, 1H, NH), 5.20 (t, *J* 9.9, 1H, H-4), 5.28 (t, *J* 10.8, 1H, H-3), 5.74 (d, *J* 8.9, 1H, H-1$_\beta$), 6.24 (d, *J* 3.3, 1H, H-1$_\alpha$).

^{13}C NMR: δ 20.7 (CH_3-Ac), 53.3 (C-2), 61.8 (C-6), 69.8 (C-4), 70.5 (C-3), 72.8 (C-5), 74.8 (C-Troc), 90.6 (C-1), 92.4 (CCl_3-Troc), 154.3 (CO-Troc), 168.8, 169.3, 170.8, 171.3.

1.3. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α,β-D-glucopyranose (4)

To a magnetically stirred solution of compound **3** (8.6 g, 16.5 mmol) in anhydrous THF (50 mL) at room temperature benzylamine (2.2 mL, 19.8 mmol) was added dropwise. Within 12 h the starting protected sugar was completely consumed (TLC monitoring). After removal of the solvent under reduced pressure, an excess of aq 1 M HCl was added to the residue and the suspension was extracted with $CHCl_3$. The organic layers were shaken with saturated aq $NaHCO_3$, washed with brine until neutral, dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. Silica-gel chromatography (hexane/AcOEt, 8:2) of the crude product gave pure **4** (6.6 g, 13.8 mmol; yield 84%). One analytical sample: oil. Calcd for $C_{15}H_{20}Cl_3NO_{10}$ (479.02): C, 37.48; H, 4.19; N, 2.91. Found: C, 37.51; H, 4.22; N, 2.98.

^{1}H NMR: δ 1.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.24 (br s, 1H, OH), 4.03 (ddd, *J* 10.3, *J* 3.5, 1H, H-2), 4.12–4.32 (m, 3H, H-5, H_a-6, H_b-6), 4.65 (d, *J* 12.0, 1H, H_a-Troc), 4.82 (d, *J* 12.0, 1H, H_b-Troc), 5.13 (t, *J* 9.4, 1H, H-4), 5.26–5.44 (m, 3H, H-1$_\beta$, H-3, NH).

^{13}C NMR: δ 20.5 (CH_3-Ac), 54.0 (C-2), 61.8 (C-6), 67.5 (C-5), 68.1 (C-4), 70.6 (C-3), 74.4 (CH_2), 91.6 (C-1), 154.0 (CO-Troc), 169.3–171.2 (CO-Ac).

1.4. 1-*O*-*tert*-Butyldiphenylsilyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (5a)

To a magnetically stirred solution of **4** (6.6 g, 13.8 mmol) in anhydrous CH_3CN (72 mL) at room temperature, solid imidazole (1.4 g, 20.7 mmol) was added in one portion, followed by *tert*-butyldiphenylchlorosilane (TBDPSCl) (5.4 mL, 20.7 mmol), added dropwise. After 12 h the solvent was removed under reduced pressure. The crude residue was dissolved in $CHCl_3$ and the solution was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under vacuum. The final product (**5a**) was eventually isolated by chromatography (hexane/AcOEt, 8:2) as an oil (8.3 g, 11.4 mmol; 83% yield). One analytical sample: oil. Calcd for $C_{31}H_{38}Cl_3NO_{10}Si$ (717.13): C, 51.78; H, 5.33; N, 1.95. Found: C, 51.82; H, 5.31; N, 2.00.

^{1}H NMR: δ 1.10 (s, 9H, 3 × CH_3-*t*-butyl), 1.96 (s, 3H, CH_3-Ac), 1.99 (s, 3H, CH_3-Ac), 2.00 (s, 3H, CH_3-Ac), 3.38 (m, 1H, H-5), 3.89 (m, 1H, H-2), 3.96 (dd, *J* 2.1, *J* 11.9, 1H, H_a-6), 4.09 (dd, *J* 5.2, *J* 11.9, 1H, H_b-6), 4.50–4.58 (m, 2H, H-1, H_a-Troc), 4.76 (d, *J* 11.9, 1H, H_b-Troc), 4.80 (d, *J* 9.8, 1H, NH), 4.98 (t, *J* 9.8, 1H, H-3), 5.40 (t, *J* 9.8, 1H, H-4), 7.30–7.80 (m, 10H, H-arom).

^{13}C NMR: δ 19.3 (C-*t*-butyl), 20.8 (CH_3-Ac), 26.9 (CH_3-*t*-butyl), 58.1 (C-2), 62.4 (C-6), 68.9 (C-4), 71.8 (C-3), 72.6 (CH_2), 74.8 (C-5), 93.9 (C-Cl_3), 96.2 (C-1), 127.7–136.2 (C-arom), 154.2 (CO-Troc), 169.6–171.0 (CO-Ac).

1.5. 1-*O*-*tert*-Butyldiphenylsilyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-amino-β-D-glucopyranoside (5b)

To a solution of compound **5a** (4.2 g, 5.9 mmol) in glacial acetic acid (0.8 L), activated Zn dust (76 g, 1.15 mmol) [washed with aq 2 M HCl, water, acetone, diethyl ether, and then dried under vacuum] was added in one portion and the mixture was vigorously stirred for 12 h (TLC monitoring) at room temperature. The solid was then filtered off and most of acetic acid was evaporated under reduced pressure. The residue was diluted with AcOEt and the resulting solution was shaken with saturated aq $NaHCO_3$, washed with brine until neutral, dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the crude residue was purified on silica gel (CH_2Cl_2/CH_3OH, 99:1) to afford the pure product **5b** (2.5 g, 4.7 mmol; 82% yield). One analytical sample: oil. Calcd for $C_{28}H_{37}NO_8Si$ (543.23): C, 61.86; H, 6.86; N, 2.58. Found: C, 61.82; H, 6.88; N, 2.60.

^{1}H NMR (400 MHz): δ 1.09 (s, 9H, 3 × CH_3-*t*-butyl), 1.95 (s, 6H, CH_3-Ac), 2.04 (s, 3H, CH_3-Ac), 2.34 (br s, 2H, NH_2), 2.98 (dd, *J* 10.2, *J* 7.8, 1H, H-2), 3.35 (m, 1H, H-5), 3.89 (dd, *J* 12.0, *J* 2.2, 1H, H_a-6), 4.04 (dd, *J* 12.0, *J* 5.7, 1H, H_b-6), 4.39 (d, *J* 7.8, 1H, H-1), 4.84 (t, *J* 9.8, 1H, H-3), 4.95 (t, *J* 9.7, 1H, H-4), 7.25–7.44 (m, 6H, H-arom), 7.65–7.69 (m, 4H, H-arom).

^{13}C NMR (100 MHz): δ 19.0 (C-*t*-butyl), 20.4 (CH_3-Ac), 26.6 (CH_3-*t*-butyl), 57.7 (C-2), 62.2 (C-6), 68.9 (C-4), 71.4 (C-3), 74.6 (C-5), 98.5 (C-1), 127.14–135.7 (C-arom), 169.6–170.6–171.5 (CO-Ac).

1.6. 1-*O*-*tert*-Butyldiphenylsilyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-[(((9*H*-fluoren-9-yl)methoxy)carbonyl) pyrrolidin-2-carboxyamido]-β-D-glucopyranoside (6)

To a magnetically stirred solution of commercial Fmoc-L-Pro-OH (3.7 g, 11.1 mmol) in anhydrous CH_2Cl_2 (59 mL) in an ice bath, HOBT (3.0 g, 22.2 mmol) was added in one portion. After 30 min, a solution of compound **5b** (5.0 g, 9.3 mmol) and EDC (18.1 mL, 10.2 mmol) in the same solvent (55 mL) was added dropwise over 5 min at the same temperature. The mixture was stirred for 12 h in an ice bath and then allowed to warm slowly to room temperature. As soon as the starting compound **5b** was completely consumed (TLC monitoring), most of the solvent was evaporated under reduced pressure and replaced by EtOAc. A precipitate was filtered off and the solution was washed with saturated aq $NaHCO_3$, brine until neutral, and then dried (Na_2SO_4). The evaporation of the solvents under reduced pressure gave a crude residue that was chromatographed on silica gel (CH_2Cl_2/Et_2O, 95:5) to afford the oily coupling product **6** (7.2 g, 8.4 mmol; 90% yield). One analytical sample: oil. Calcd for $C_{48}H_{54}N_2O_{11}Si$ (862.35): C, 66.80; H, 6.31; N, 3.25. Found: C, 66.83; H, 6.32; N, 3.29.

^{1}H NMR: δ 1.03 (s, 9H, 3 × CH_3-*t*-butyl), 1.80–1.85 (m, 3H, H-4′, H_a-3′), 1.93 (s, 9H, CH_3-Ac), 2.29 (m, 1H, H_b-3′), 3.29–3.44 (m, 3H, H-5, H-5′), 3.83–3.87 (m, 2H, H_a-6, H-2), 4.00 (dd, 1H, *J* 12.0, *J* 5.5, H_b-6), 4.17–4.34 (m, 3H, H-2′, H-Fmoc, CH_a-Fmoc), 4.46 (m, 1H, CH_b-Fmoc), 4.81 (d, 1H, *J* 6.8, H-1), 4.97 (t, 1H, *J* 9.6, H-4), 5.17 (t, 1H, *J* 9.6, H-3), 6.92 (d, 1H, *J* 8.0, NH), 7.30–7.80 (m, 18H, H-arom).

^{13}C NMR: δ 18.7 (C-*t*-butyl), 20.1 (CH_3-Ac), 24.1 (C-4′), 26.3 (CH_3-*t*-butyl), 27.4 (C-3′), 46.7 (CH-Fmoc), 46.7 (C-5′), 56.2 (C-2), 60.2 (C-2′), 61.8 (C-6), 67.3 (CH_2-Fmoc), 68.5 (C-4), 71.0 (C-5), 71.3 (C-3), 95.2 (C-1), 119.6–140.9 (C-arom), 143.4 (C-Fmoc), 168.9–170.0 (CO-Ac), 172.6 (CONH).

1.7. (2*S*)-*N*-((2*S*,3*S*,4*R*,5*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)pyrrolidine-2-carboxamide (1)

Compound **6** was dissolved by a saturated solution of NH_3 in dry MeOH (43 mL), in ice bath and under magnetic stirring. After 12 h, **6** was completely consumed (TLC monitoring). The solvent was co-evaporated with Et_2O under reduced pressure to afford a residue that was eventually chromatographed on silica gel ($CHCl_3$/CH_3OH, 95:5) to obtain the final product **1**. The latter was purified by HPLC (FlowLab Semipreparative HPLC System) on Phenomenex Axia Packed Luna C18(2) column: 50 × 21.20 mm, 5 μm, 100 Å, using H_2O/MeCN/TFA (97:3:0.1) [eluent A] and MeCN/H_2O/TFA (80:20:0.1) [eluent B] gradient system with a flow rate of 12 mL min^{-1}. Final yield: 2.7 g, 5.3 mmol; 75%. One analytical sample: mp 71.8–72.0 °C; $[\alpha]_D^{25}$ −12.6 (*c* 2.5 in MeOH). Calcd for

$C_{27}H_{38}N_2O_6Si$ (514.25): C, 63.01; H, 7.44; N, 5.44. Found: C, 62.98; H, 7.41; N, 5.43.

^1H NMR (CD_3OD): δ 1.05 (s, 9H, CH_3-*t*-butyl), 1.93–2.05 (m, 2H, H-4′), 2.11 (m, 1H, H_a-3′), 2.36 (m, 1H, H_b-3′), 2.98 (m, 1H, H-5), 3.34–3.42 (m, 4H, H-3, H-4, H-5′), 3.61 (dd, *J* 11.6, *J* 4.7 Hz, 1H, H_a-6), 3.70 (dd, *J* 11.6, *J* 2.8 Hz, 1H, H_b-6), 3.81 (dt, *J* 7.9, *J* 1.9 Hz, 1H, H-2), 3.99 (m, 1H. H-2′), 4.67 (d, *J* 8.4 Hz, 1H, H-1), 7.28–7.50 (m, 6H, H-arom), 7.61–7.77 (m, 4H, H-arom).

^{13}C NMR (CD_3OD): δ 24.9 (C-4′), 27.4 (C-*t*-butyl), 31.3 (C-3′), 47.6 (C-5′), 59.8 (C-2), 61.2 (C-2′), 62.6 (C-6), 72.2 (C-4), 75.7 (C-3), 77.8 (C-5), 97.4 (C-1), 128.6, 131.1, 134.7, 137.2 (C-arom), 169.8 (CO).

HRMS-TOF Calcd for $C_{27}H_{38}N_2O_6Si$ [M+Na^+]: 537.6742. Found: 537.6744.

1.8. General procedure for cyclohexanone/miscellaneous benzaldehydes aldol reactions catalyzed by 1

Into an 8 mL Wheaton clear glass/screw cap vial, solid **1** (7.7 mg, 1.5×10^{-2} mmol) suspended in brine (or THF) (1 mL), cyclohexanone (3.0 mmol), and the aldehyde under investigation (0.75 mmol) were poured in sequence. The mixture was vigorously stirred in the stoppered vial at the chosen temperature/time (cf. Tables 1 and 2). After quenching by 20% aq NH_4Cl (4 mL) and extraction with Et_2O (3×5 mL), the organic layers were washed with brine and dried (Na_2SO_4). The combined water extracts containing salts and most of the recovered catalyst were freeze-dried and put aside. Evaporation of the solvents under reduced pressure gave a crude residue that was adsorbed on a preparative layer plate eluting twice with hexane/EtOAc (7:3) to get residual starting aldehyde and *anti* plus *syn* couples. The *anti:syn* ratio was determined by 500 MHz ^1H NMR. The *anti* ee was determined by HPLC on chiral column (Daicel, Chiralpak, IC).

All the experiments were duplicated.

The solid coming from freeze-dried water extracts was poured onto a short silica gel column and eluted with $CHCl_3$/MeOH (8:2). The crude organic product thus obtained was then purified by preparative HPLC, as reported for the isolation of **1**. Recovery range: 72–89% (when 2 mol % used, cf. Table 3).

1.9. Racemization assessment of the enantiomeric *anti* aldols 2

Into an 8 mL Wheaton clear glass/screw cap vial, solid **1** (2.6 mg, 5×10^{-3} mmol) and an authentic mixture (98:2; 2.5 mmol) of the *anti* enantiomeric aldols, coming from the reaction of cyclohexanone and 4-nitrobenzaldehyde, were suspended in brine (1 mL). The mixture was vigorously stirred in the stoppered vial at 25 °C for 48 h. After extraction with Et_2O (3×5 mL) of the crude reaction mixture, the organic layers were washed with brine and dried (Na_2SO_4). The combined water extracts containing salts and most of the recovered catalyst were freeze-dried and put aside. Evaporation of the solvents under reduced pressure gave a crude residue that was analyzed by HPLC on chiral column (Daicel, Chiralpak, IC). The mixture turned out to be unchanged (98:2).

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Supplementary data

Supplementary data (^1H and ^{13}C spectra, HPLC conditions and area graphs) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.03.041.

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