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Methyl 12-[D-prolinoylamino]cholate as a versatile organocatalyst for the asymmetric aldol reaction of cyclic ketones

Gian Luigi Puleo[a,b] and Anna Iuliano[b,*]

[a]*Scuola Normale Superiore di Pisa, Piazza dei Cavalieri 7, 56126 Pisa, Italy*
[b]*Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy*

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Abstract—The use of cholic acid derivative **1**, bearing a D-prolinamide moiety linked at the 12-position of cholic acid methylester, as an organocatalyst in the asymmetric aldol reaction of cyclic ketones and aromatic aldehydes, gave the corresponding aldol products in good yield and ee up to 98%. This organocatalyst has proven to be efficient both in water and in organic solvent, where it has been used with a 1% loading.

1. Introduction

Since the seminal paper of List et al.[1] demonstrated that proline and proline analogues promote the asymmetric direct aldol reaction with good enantioselectivities, several efforts have been directed towards the synthesis of different organocatalytic systems able to afford high levels of asymmetric induction in this reaction. The formation of C–C bonds via diastereoselective and enantioselective ways to afford products having both keto and hydroxyl groups,[2] easily explains the interest towards the asymmetric aldol reaction. In addition, the organocatalytic version of this chemical transformation offers the advantage of being environmentally friendly, since no metal species are involved, and the reaction can be performed without the use of an inert atmosphere or absolute solvents.[3] These last considerations have prompted scientists to search for organocatalytic systems that can work under very environmentally benign conditions, that is, low catalyst loading or using water as reaction solvent. Many efforts have been addressed towards the synthesis of such appealing organocatalysts that have produced systems able to afford very good stereoselectivities under such type of conditions.[4] However, the achievement of a versatile organocatalyst, able to work with low catalyst loading or in water still remains a challenge. In fact, it often happens that the use of water as a solvent requires the presence of acid or salt additives[5] in order for the organocatalyst to be efficient, or that a large excess of the donor carbonyl compound is mandatory to perform the reaction.[6] In addition, it is difficult to find an organocatalytic system that works both in water and in organic solvents, conditions that would permit a wider applicability of the chiral auxiliary.

We have recently synthesised a new family of asymmetric organocatalysts, by linking the prolinamide moiety to the different functionalised positions of cholic and deoxycholic acids.[7] The preliminary study aimed at verifying the capability of these systems to work as organocatalysts in the direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde showed that the best combination position on the cholestanic backbone-absolute configuration of the prolinamide moiety is obtained when the D-prolinamide unit is linked at the 12-position of the bile acids; in addition, the presence of free hydroxyl groups at the 3- and 7-positions guaranteed the achievement of good levels of asymmetric induction.[7] Indeed, derivative **1** (Fig. 1), possessing these structural features, emerged as the best asymmetric organocatalyst, giving ees up to 80%.[7] Its effectiveness is attributable to the unique structure of cholic acid, which gives rise, with the appended proline moiety, to a chiral cavity, where the position of the aldehyde substrate is controlled by the free hydroxyl groups.[7]

These encouraging results prompted us to extend the use of this organocatalyst to the reaction of other substrates and

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[*] Corresponding author. Tel.: +39 0502219231; fax: +39 0502219260; e-mail: iuliano@dcci.unipi.it

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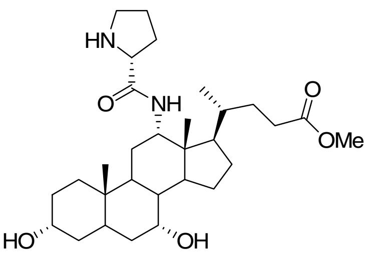

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Figure 1. Chemical structure of organocatalyst **1**.

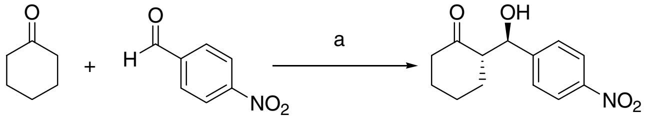
to verify the possibility of performing the reaction using water as solvent and low catalyst loading. Herein, we report the results obtained using **1** as an organocatalyst in the asymmetric direct aldol reaction of cyclic ketones and various aromatic aldehydes, the evaluation of its effectiveness both in organic solvents and in water, as well as the possibility of performing the reaction with very low catalyst loading.

2. Results and discussion

The reaction between cyclohexanone and 4-nitrobenzaldehyde, using **1** as an organocatalyst, was performed according to the 'pre-activation' method, which involves the mixing of the ketone and **1** at reaction temperature for 1 hour, followed by the addition of the aldehyde.[8] The effect of different reaction parameters, such as solvent, catalyst loading, amount of ketone and temperature, was investigated and the results are reported in Table 1.

The use of a 1:2 H_2O/DMF mixture, the solvent giving the best result with acetone as the donor substrate,[7] with a 5% catalyst loading at room temperature and using only a twofold excess of ketone, afforded complete conversion of the aldehyde substrate in 24 h (entry 1). The aldol product was obtained with low diastereoselectivity in favour of the *anti*-isomer, which showed a 77% ee (entry 1). Lowering the temperature to 0 °C (entry 2) caused an improvement of both diastereoselectivity, which went to 80%, and enantioselectivity of the *anti*-isomer, which was obtained in 87% ee. This good result was flanked by a slowing down of the reaction rate, with 70% of substrate conversion being obtained. Further lowering of the reaction temperature to −20 °C (entry 3) slightly improved both the diastereoisomeric and enantiomeric excesses, but slowed down the reaction rate so that only a 50% conversion was obtained in 24 h. Screening of various organic solvents (entries 4–8) showed that the best results in terms of conversion of the substrate as well as stereoselectivity were obtained when non-competing hydrogen bonding solvents, such as toluene, nitrobenzene or dichloromethane, were used. As a matter of fact, the use of methanol, a protic solvent, caused a decrease in both conversion and asymmetric induction (entry 4). It is also noteworthy that toluene, a π-rich aromatic solvent, and nitrobenzene, a π-acceptor aromatic solvent, gave the same results, allowing us to conclude that no π–π stacking between solvent molecules and aldehyde substrate was involved in determining the outcome of the reaction. It seems likely that the organic solvent only acts as a diffusion medium, when it cannot interact with the substrate or the organocatalyst by means of hydrogen bonds. As a matter of fact, worsening of the

Table 1. Reaction of 4-nitrobenzaldehyde with cyclohexanone in the presence of organocatalyst **1**[a]



Entry	Cat. (%)	Solvent	Temp (°C)	Time (h)	Conv.[c] (%)	de (%) (*anti*)[c]	ee[b] (%)
1	5	H_2O/DMF[d]	rt	24	>98	28	77
2	5	H_2O/DMF[d]	0	24	70	80	87
3	5	H_2O/DMF[d]	−20	24	50	82	90
4	5	MeOH	0	24	46	82	63
5	5	DMF	0	24	28	83	87
6	5	Toluene	0	24	97	83	85
7	5	Nitrobenzene	0	24	>98	84	86
8	5	DCM	0	24	>98	84	86
9	5	H_2O[e]	0	48	61	80	81
10	2	H_2O[e]	0	96	31	85	68
11	5	H_2O[e]	0	96	12[f]	95	68
12	2	DCM	0	48	>98	92	87
13	1	DCM	0	48	>98	94	87
14	5	H_2O/DMF[d]	0	48	>98	46	60[g]

[a] Reagents and conditions: *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (0.5 mmol), catalyst, solvent (usually 0.5 mL); reactions were monitored by TLC.

[b] Determined by HPLC on chiral stationary phase (Chiralpack AS, hexane/2-propanol 85:15, 1 mL/min, 254 nm); main diastereoisomer was *anti*.

[c] Determined by ^1H NMR.

[d] H_2O/DMF 1:2.

[e] All these reactions were performed in 2 mL of H_2O.

[f] 1 equiv of ketone was used.

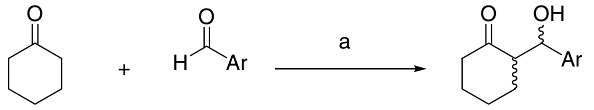
[g] Organocatalyst with L-Pro was used; the opposite enantiomer was obtained in prevalence.

reaction outcome occurs using a protic solvent (DMF, entry 5, caused only slowing down of the reaction rate), probably because the hydrogen bonds between the solvent and aldehyde substrate or organocatalytic species compete with the hydrogen bonds between the reactive enamine species of the organocatalyst and the aldehyde, which are believed to be important for the stereoselectivity of the reaction.[9] Water behaved in a different way (entry 9): although the reaction was slower, when performed in pure water as a solvent, a good level of asymmetric induction was obtained. This is not surprising if we take into account that water does not solubilise either the reagents or organocatalysts. The hydrophobic components are obliged by water to react in a 'concentrated organic medium':[10] in this sense water does not compete for hydrogen bonds, behaving as, for example, dichloromethane and guarantees the achievement of good ees. Decreasing the catalyst loading or ketone amount had a detrimental effect on both the reaction rate and the asymmetric induction (entries 10 and 11). Conversely, lowering of the catalyst loading in dichloromethane solution did not affect the extent of the asymmetric induction, or the reaction rate (entries 12 and 13). The aldol reaction between 4-nitrobenzaldehyde and cyclohexanone can be carried out using a very low amount of **1** (1%), without a loss in catalytic efficiency or asymmetric induction: in addition, the low catalyst loading had a positive effect on the diastereoselectivity of the reaction, with the aldol product being obtained in 94% de (entry 13). The use of the diastereoisomeric analogue of **1**, which possesses an L-prolinamide moiety linked at the 12-position of cholic acid, gave the aldol product in high yield but in lower enantiomeric excess (entry 14), suggesting that the more effective diastereoisomer is obtained when the D-proline moiety is linked at the 12-position of cholic acid. The opposite enantiomer of the *anti*-product was obtained in prevalence: this result suggests that the sense of asymmetric induction is governed by the proline moiety linked to the 12-position of the cholic acid.

The conditions giving the best results in the asymmetric aldol reaction of cyclohexanone and 4-nitrobenzaldehyde, that is, water with 5% catalyst loading and dichloromethane with 1% of **1** at 0 °C, were used to test the reaction with other substrates. The results concerning the aldol reaction of cyclohexanone and various aromatic aldehydes are reported in Table 2. The reactions carried out in water (entries 1–6) were faster than those performed in dichloromethane (entries 7–11) independently of the aldehyde substrate. This can be attributed mainly to the different catalyst loading that has a scarce influence in the case of the reaction of 4-nitrobenzaldehyde but affects to a greater extent the reaction of other kind of aldehyde substrates.

The extent of the substrate conversion depended on the electrophilic character of the aromatic aldehyde as well as the steric hindrance near the carbonyl group in both the solvents: as a matter of fact that benzaldehyde and 2-nitrobenzaldehyde gave a lower conversion (entry 5) or required longer reaction times to afford good conversions (entries 6, 10 and 11). Only 4-chlorobenzaldehyde, an electrophilic and unhindered substrate, exhibited an unusual behaviour (in water), giving a 58% conversion (entry 2). Both the diastereomeric and enantiomeric ratios were affected by the solvent in an opposite way: water gave very high diastereoisomeric excess in favour of *anti*-diastereoisomer (entries 1–6), whereas the highest enantiomeric excesses were obtained by performing the reaction in dichloromethane solution (entries 7–11). The extent of asymmetric induction depended on the nature of the aldehyde substrate to a

Table 2. Reaction of aromatic aldehydes with cyclohexanone in the presence of organocatalyst **1**[a]



Entry	Ar	Solvent	Catalyst (mol %)	Time (h)	Conv.[c] (%)	de[c] (%)	ee[b] (%)
1	4-FC_6H_4	H_2O[d]	5	48	95	94	81[f]
2	4-ClC_6H_4	H_2O[d]	5	48	58	84	68[f]
3	4-$CF_3C_6H_4$	H_2O[d]	5	48	>98	97	63[g]
4	2-ClC_6H_4	H_2O[d]	5	48	93	95	62[h]
5	2-$NO_2C_6H_4$	H_2O[d]	5	48	46	99	62[g]
6	Ph	H_2O[d]	5	72	61	80	80[h]
7	4-FC_6H_4	DCM[e]	1	120	>98	80	80[f]
8	4-ClC_6H_4	DCM[e]	1	120	80	83	90[f]
9	4-$CF_3C_6H_4$	DCM[e]	1	48	74	85	84[g]
10	2-$NO_2C_6H_4$	DCM[e]	1	120	76	95	80[g]
11	Ph	DCM[e]	1	120	81	26	80[h]

[a] Reagents and conditions: aldehyde (0.25 mmol), cyclohexanone (0.5 mmol), catalyst, solvent at 0 °C.

[b] Enantiomeric excess of the *anti* = diastereoisomer.

[c] Determined by ^1H NMR; main diastereoisomers were *anti*.

[d] All these reactions were performed in 2 mL of H_2O.

[e] All these reactions were performed in 0.5 mL of DCM.

[f] Determined by HPLC analyses on Chiralpack AD, 254 nm, hexane/2-propanol 90:10, 0.5 mL/min.

[g] Chiralcel OD-H, 254 nm, hexane/2-propanol 95:5, 1 mL/min.

[h] Chiralcel OD-H, 210 nm, hexane/2-propanol 99:1, 0.4 mL/min.

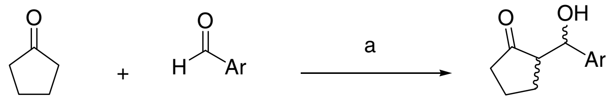
greater extent in water than in dichloromethane: aldehyde possessing a less polarisable aromatic ring gave the highest enantiomeric excess in water (entries 1 and 6), whereas the ees in dichloromethane were around the 80% value (entries 7, 9–11) except for 4-chlorobenzaldehyde, which afforded the aldol product in 90% ee (entry 8).

The same conditions were used in the aldol reaction of cyclopentanone and various aromatic aldehydes: the results are reported in Table 3.

The conversions of the aldehyde substrates were similar in water and in dichloromethane, except for 2-chlorobenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde, which gave remarkably higher conversions in water (entries 8, 10 and 14).

Conversions with this ketone also depended on the electronic nature of the aldehyde as well as on the steric hindrance near the carbonyl group (entries 5–7 and 12–14), with the sole exception of the reaction of 4-nitrobenzaldehyde in dichloromethane (entry 1).[11] As far as the diastereoisomeric ratios are concerned, low diastereoisomeric prevalence was observed in all the cases: this is not surprising, given that the use of cyclopentanone as a donor substrate usually affords low diastereoisomeric excesses.[12] However, it should be noted that in most cases the diastereoisomeric ratios are higher than those reported with other proline-derived organocatalysts.[12] The reactions performed in dichloromethane gave a prevalence of the *anti*-diastereoisomer, except when 2-nitro and 2-chlorobenzaldehyde were used as substrates, suggesting that *ortho*-substitution is a structural feature that helps the formation of the *syn*-isomer. In contrast, when water was used as reaction solvent, prevalence of the *syn*-isomer was obtained, apart from the reaction of benzaldehyde (entry 12) that still gave a prevalence of the *anti*-isomer, but to a remarkably lower extent. These results suggest that water can stabilise the transition state leading to the formation of the *syn*-product: such a kind of stabilisation gives rise to inversion of the diastereoisomeric ratio (entries 8–11), or to a lower prevalence of the *anti*-product (entry 12) or to a higher prevalence of the *syn*-isomer (entries 13 and 14), in passing from dichloromethane to water. The *anti*-products were obtained in good enantiomeric excesses in both solvents, apart from the reactions of 2- and 4-chlorobenzaldehyde in water (entries 10 and 14): as observed in the case of cyclohexanone, the best asymmetric inductions were achieved when the reaction was performed in dichloromethane (entries 1–7). On the contrary, the enantiomeric excesses of the *syn*-products were lower and a general trend depending on the solvent cannot be found: the *syn*-product coming from the reaction of benzaldehyde was obtained in 62% ee in dichloromethane (entry 5), whereas a 60% ee of the *syn*-product coming from the reaction of 4-nitrobenzaldehyde was obtained in water (entry 8). The sense of asymmetric induction, as far as the *anti*-product was concerned, changed in passing from dichloromethane to water

Table 3. Reaction of aromatic aldehydes with cyclopentanone in the presence of organocatalyst **1**[a]



Entry	Ar	Solvent	Catalyst (mol %)	Conv.[c] (%)	dr[c] (%) (*anti*:*syn*)	er[b] (%) (*anti*)	er[b] (%) (*syn*)
1	4-$NO_2C_6H_4$	DCM[d]	1	36	69:31	97:3[g]	55:45[g]
2	4-FC_6H_4	DCM[d]	1	>98	53:47	93:7[h]	65:35[h]
3	4-ClC_6H_4	DCM[d]	1	83	54:46	90:10[g]	67:33[g]
4	4-$CF_3C_6H_4$	DCM[d]	1	>98	69:31	99:1[i]	71:29[i]
5	Ph	DCM[d,f]	1	93	72:28	95:5[j]	81:19[j]
6	2-$NO_2C_6H_4$	DCM[d]	1	53	43:57	97:3[k]	65:35[k]
7	2-ClC_6H_4	DCM[d]	1	51	44:56	95:5[l]	72:28[l]
8	4-$NO_2C_6H_4$	H_2O[e]	5	>98	41:59	98:2[g]	20:80[g]
9	4-FC_6H_4	H_2O[e]	5	89	39:61	80:20[h]	44:56[h]
10	4-ClC_6H_4	H_2O[e]	5	>98	41:59	73:27[g]	47:53[g]
11	4-$CF_3C_6H_4$	H_2O[e]	5	>98	36:63	95:5[i]	36:64[i]
12	Ph	H_2O[e,f]	5	87	54:46	5:95[j]	53:47[j]
13	2-$NO_2C_6H_4$	H_2O[e]	5	57	33:67	94:6[k]	72:28[k]
14	2-ClC_6H_4	H_2O[e]	5	91	28:72	41:59[l]	35:65[l]

[a] Reagents and conditions: aldehyde (0.25 mmol), cyclopentanone (0.5 mmol), catalyst, solvent at 0 °C for 60 h.

[b] Enantiomeric ratio: first eluted enantiomer:second eluted enantiomer.

[c] Determined by ^1H NMR.

[d] All these reactions were performed in 0.5 mL of DCM.

[e] All these reactions were performed in 2 mL of H_2O.

[f] Reaction time: 96 h.

[g] Determined by HPLC analyses on Chiralpack AS, 254 nm, hexane/2-propanol 85:15, 1 mL/min.

[h] Chiralpack AD, 210 nm, hexane/2-propanol 95:5, 0.5 mL/min.

[i] Chiralpack AD, 254 nm, hexane/2-propanol 90:10, 0.5 mL/min.

[j] Chiralcel OD-H, 210 nm, hexane/2-propanol 90:10, 0.5 mL/min.

[k] Chiralcel OD-H, 254 nm, hexane/2-propanol 95:5, 1 mL/min.

[l] Chiralpack AD, 220 nm, hexane/2-propanol 99.5:0.5, 1 mL/min.

in the case of benzaldehyde and 2-chlorobenzaldehyde (entries 5, 7, 12 and 14). As far as the *syn*-product was concerned, the opposite enantiomer was obtained in prevalence in water in several cases (entries 8–11). These results point to a change of asymmetric induction mechanism depending on the solvent with some aldehyde substrates. This particular behaviour of organocatalyst **1** is very useful when benzaldehyde is reacted: actually, both enantiomers of the *anti*-aldol product can be obtained in 90% ee simply by changing the reaction solvent (entries 5 and 12).

3. Conclusion

The bile acid derivative **1**, bearing a D-prolinamide moiety linked at the 12-position of cholic acid methylester, has proven to be an efficient organocatalyst for the asymmetric direct aldol reaction of cyclic ketones and aromatic aldehydes, affording aldol products in good yield and ees up to 98%. This organocatalyst showed high versatility, giving good results both in water and in organic solvents, where it also works when used with 1% loading, without loss of stereoselectivity, conditions that rarely afford good results.[4f,g] Organocatalyst **1** also afforded the highest diastereoisomeric ratios reported until now in the aldol reactions of cyclopentanone. The sense of asymmetric induction is governed by the proline moiety and, when cyclopentanone is used as a carbonyl donor, it also depended on the solvent. This unusual behaviour, which can be likely attributed to a change of asymmetric induction mechanism depending on the solvent, allows both enantiomers of an aldol product to be obtained starting from the same chiral organocatalyst, simply by changing the reaction solvent.

4. Experimental

4.1. General procedures and materials

TLC analyses were performed on silica gel 60 sheets; flash chromatography separations were carried out on columns using silica gel 60 (230–400 mesh). CH_2Cl_2 and *N*-methylmorpholine were refluxed over CaH_2 and distilled before use. MeOH was refluxed over magnesium methoxide and distilled before the use. MeONa was prepared immediately before the use with dry MeOH and metallic Na at 0 °C. Unless otherwise specified, the reagents were used without any purification. Methyl-3α,7α-diacetyloxy-12α-amino-5β-cholan-24-oate and methyl-3α,7α-dihydroxy-12α-*N*-(D-prolinoyl)amino-5β-cholan-24-oate, **1**, were obtained as previously described and matched the reported characteristics.[7]

4.2. Instrumentation

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 300 MHz NMR spectrometer, using TMS as the external standard. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br = broad. HPLC analyses were performed on a JASCO PU-980 intelligent HPLC pump equipped with JASCO UV-975 detector. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Melting points were taken using a Kopfler Reichert–Jung apparatus. IR spectra were recorded on a Perkin–Elmer 1710 spectrophotometer.

4.3. Synthesis of organocatalyst

4.3.1. Methyl-3α,7α-diacetyloxy-12α-*N*-(L-Boc-prolinoyl)-amino-5β-cholan-24-oate. *N*-Methylmorpholine (135 μL, 1.22 mmol) was added to a solution of *N*-Boc protected proline (236 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (8 mL), and the mixture was cooled to −20 °C, then isobutylchloroformate (143 μL, 1.1 mmol) was added. The reaction temperature was maintained at −20 °C for 5 min, then a CH_2Cl_2 solution of methyl-3α,7α-diacetyloxy-12α-amino-5β-cholan-24-oate (506 mg, 1 mmol) was added dropwise over 15 min at 0 °C. The reaction mixture was stirred for 26 h, then treated with HCl aq, $NaHCO_3$ aq, NaCl aq and dried over anhydrous Na_2SO_4. The organic phases were concentrated in vacuo and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2/acetone 93:7). Yield 250 mg, 36%. Mp 57–59 °C $[\alpha]_D^{22} = +28.3$ (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (s, 3H, CH_3), 0.89 (d, 3H, 21-CH_3), 0.93 (s, 3H, CH_3), 1.00–2.60 (m, 28H, steroidal CH and CH_2, and 3′ and 4′-CH_2 of Boc-Pro), 1.48 (s, 9H, Boc-3CH_3), 1.98 (s, 3H, 3-CH_3CO), 2.10 (s, 3H, 7-CH_3CO), 3.47 (m, 2H, 5′-CH_2 of Boc-Pro), 3.64 (s, 3H, CH_3OCO), 4.25 (br d, 1H, 2′-CH of Boc-Pro), 4.34 (br s, 1H, 12-CH), 4.57 (m, 1H, 3-CH), 4.91 (br s, 1H, 7-CH) 6.71 (br s, NH amide). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 17.4, 21.6, 21.8, 22.8, 23.4, 24.5, 26.3, 26.9, 27.4, 28.7, 29.5, 30.8, 31.4, 34.6, 34.8, 34.9, 38.2, 40.9, 44.6, 47.4, 48.6, 51.5, 51.6, 61.1, 71.1, 73.8, 80.6, 155.4, 170.3, 170.7, 170.9, 174.8. IR (KBr, cm^{-1}): 2950, 2872, 1738, 1654, 1516, 1431, 1364, 1246, 1180, 1070, 921, 852.

4.3.2. Methyl-3α,7α-dihydroxy-12α-*N*-(Boc-L-prolinoyl)-amino-5β-cholan-24-oate. Methyl-3α,7α-diacetyloxy-12α-*N*-(L-Boc-prolinoyl)amino-5β-cholan-24-oate (190 mg, 0.275 mmol) was treated with MeONa solution 10% in MeOH (1.25 mL) for 6 h at rt. The reaction was quenched in aqueous HCl, extracted with CH_2Cl_2 and dried over Na_2SO_4. Organic phases were concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/acetone 6:4). Yield 66 mg, 39%. Mp 95–98 °C. $[\alpha]_D^{22} = +15.3$ (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3), 0.87 (d, 3H, 21-CH_3), 0.89 (s, 3H, CH_3), 1.10–2.60 (m, 28H, steroidal CH and CH_2, and 3′ and 4′-CH_2 of Boc-Pro), 1.47 (s, 9H, Boc-3CH_3), 3.40 (m, 2H, 5′-CH_2 of Pro), 3.49 (m, 1H, 3-CH) 3.64 (s, 3H, CH_3OCO), 3.84 (br s, 1H, 12-CH), 4.27 (br s, 1H, 7-CH), 7.15 (br s, NH amide). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 17.4, 22.6, 23.4, 24.3, 26.0 27.5, 28.6, 29.4, 30.8, 30.9, 31.3, 34.7, 34.8, 35.1, 35.3, 39.6, 40.1, 41.5, 44.1, 44.4, 47.3, 48.7, 51.5, 51.9, 60.6, 68.2, 71.9, 80.8, 155.7, 171.2, 174.7.

4.3.3. Methyl-3α,7α-dihydroxyl-12α-(L-prolinoyl)amino-5β-cholan-24-oate. A solution of methyl-3α,7α-dihydroxy-12α-*N*-(Boc-L-prolinoyl)amino-5β-cholan-24-oate (66 mg, 0.275 mmol) in CH_2Cl_2 (5 mL) was treated with a large excess of TFA (2 mL) and stirred at rt for 15 min. The reaction mixture was washed with 5% $NaHCO_3$ to remove the excess of acid and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with brine (3 × 50 mL) then dried over anhydrous Na_2SO_4. Organic phases were concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, AcOEt/MeOH 7:3).Yield 25 mg, 38%. Mp 103–105 °C. $[\alpha]^{22}_{D} = +28.3$ (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (s, 3H, CH_3), 0.83 (d, 3H, 21-CH_3), 0.88 (s, 3H, CH_3), 0.90–2.70 (m, 28H, steroidal CH and CH_2, and 3′ and 4′-CH_2 of Pro), 3.12 (m, 2H, 5′-CH_2 of Pro), 3.45 (m, 1H, 3-CH), 3.65 (s, 3H, CH_3OCO), 3.87 (br s, 1H, 12-CH), 4.00 (br s, 1H, 2′-CH Pro), 4.25 (br s, 1H, 7-CH), 8.32 (br s, NH amide). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 17.5, 22.6, 23.4, 25.6, 26.6, 27.6, 30.8, 31.1, 31.4, 34.8, 34.9, 35.0, 35.2, 39.3, 39.6, 41.5, 43.8, 44.6, 47.2, 48.7, 51.5, 52.1, 60.6, 68.2, 70.3, 71.9, 171.8, 174.6. IR (KBr, cm^{-1}): 2944, 2864, 1734, 1714, 1658, 1648, 1623, 1573, 1543, 1508, 1437, 1382, 1261, 1166, 1075, 985.

4.4. General procedure for aldol reaction

The organocatalyst (usually 5%) was stirred in 0.5 mL of solvent with ketone (0.5 mmol) for 1 h. Aromatic aldehyde (0.25 mmol) was added and the mixture was stirred at the indicated temperature for the indicated time. This solution was quenched in aqueous NH_4Cl (1 mL) and extracted with AcOEt (1 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified over a small column of silica gel (AcOEt/hexane 1:1) and after concentration analysed with HPLC and ^1H NMR. All the known aldol adducts matched the reported characteristics.[4–6]

4.4.1. 2-(Hydroxy-(*p*-fluoro)methyl)cyclopentan-1-one. *syn*-Diastereoisomer ^1H NMR (200 MHz, $CDCl_3$) δ: 1.28–2.52 (m, 6H, CH_2 cyclopentanone), 2.71 (dd, $J_1 = 11.4$ Hz, $J_2 = 4.4$ Hz 1H, C*H*CHOH), 4.63 (s, 1H, CHCHO*H*), 5.29 (d, 1H, $J = 2.8$ Hz, CHC*H*OH) 7.04 (t, $J = 7.8$ Hz, 2H, aromatic), 7.30 (dd, $J_1 = 6.0$ Hz, $J_2 = 2.6$ Hz, 2H, aromatic). Anal. Calcd for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29; F, 9.12; O, 15.37. Found:, 69.32; H, 6.44; F, 9.07; O, 15.50. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (95:5 hexane/2-propanol), rt, 220 nm, 0.5 mL/min; *syn*-diastereoisomer: $t_R = 22.55$ min, $t_R = 27.47$ min; *anti*-diastereomer: $t_R = 31.69$ min, $t_R = 35.72$ min.

4.4.2. 2-(Hydroxy-(*p*-chloro)methyl)cyclopentan-1-one. *syn*-Diastereoisomer ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22–2.38 (m, 6H, CH_2 cyclopentanone), 2.90 (t, $J = 13.2$ Hz 1H, C*H*CHOH), 4.63 (s, 1H, CHCHO*H*), 5.23 (br s, 1H, CHC*H*OH) 7.32 (dd, $J_1 = 22.8$ Hz, $J_2 = 8.4$ 4H, aromatic). Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78; O, 14.24. Found:, 64.12; H, 5.88; Cl, 15.90; O, 14.30. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (90:10 hexane/2-propanol), rt, 220 nm, 1 mL/min; *syn*-diastereoisomer: $t_R = 12.35$ min, $t_R = 14.65$ min; *anti*-diastereoisomer: $t_r = 16.85$ min, $t_R = 21.11$ min.

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