Solvent-Free Stereoselective Organocatalyzed Aldol Reaction of 2-Hydroxycyclobutanone

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Abstract: The stereoselective solvent-free organocatalyzed aldol reaction of 2-hydroxycyclobutanone with a selection of aromatic aldehydes has been investigated. Using L-threonine (20 mol%), deracemized aldol adducts featuring a chiral quaternary center were obtained in yields up to 72%, with *syn* selectivity up to 85:15 and ee up to 84%. The title compound has markedly superior reactivity to other α-hydroxy ketones.

Key words: cyclobutanone, L-threonine, organocatalysis, aldol reaction, stereoselective reaction

2-Hydroxycyclobutanone (**1**) is a readily available, compact molecular building block with two synthetically useful functional groups.[1] Interesting applications include ring cleavage and methylation to furnish an ester aldehyde,[2] one-pot Wittig reaction–acetalization to give an oxabicyclo[3.2.0]heptane,[3] and the preparation of methylenecyclobutane nucleoside analogues.[4] Nonetheless, the title compound remains underexploited in organic synthesis. Recently, we discovered that **1** undergoes direct aldol condensation with *p*-nitrobenzaldehyde (**2a**) in the presence of selected primary L-amino acids.[5] In wet DMF solvent, the reaction furnishes the adduct **3a** with noteworthy regio- and stereoselectivities, with the *anti* diastereomer predominating.

To further develop this original deracemizing reaction of **1**, we decided to examine the direct aldol reaction in solvent-free conditions, which constitute an increasingly important consideration in organic synthesis.[6] Some organocatalyzed solvent-free direct aldol reactions have been described,[7] but not with respect to ketone substrates having either a four-membered-ring skeleton nor an α-hydroxy function. Among the primary amino acids emerging as stereoselective organocatalysts,[8] L-threonine (L-Thr) and its derivatives have been employed successfully in solution-state direct aldol condensations,[9] so we decided to examine this amino acid's ability to mediate the solvent-free aldol reaction of **1**. The general reaction is shown in Scheme 1, and results are collected in Table 1.

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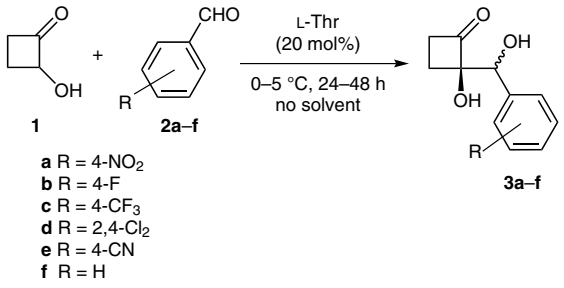
The first round of experiments, designed to screen the reaction conditions (Table 1, entries 1–3), were carried out on the prototype reaction of **1** with *p*-nitrobenzaldehyde (**2a**) in the presence of 20 mol% L-Thr. In wet DMF at room temperature, the reaction was very sluggish (25% yield of aldol **3a** after one week) and gave a preference for the *anti* isomer. In solvent-free conditions at 25 °C, the aldol was obtained in 70% yield in only six hours; again with a preference for the *anti* stereoisomer (dr = 60:40). In this case, the *syn* component had an attractive enantiomeric excess of 81%. When the solvent-free reaction was conducted again at 0–5 °C, it progressed more slowly but the aldol **3a** was obtained in 72% yield after 24 hours (Table 1, entry 3). Unexpectedly, the diastereoselectivity was inversed: the *syn* isomer now predominated (dr = 61:39), without compromise its enantiomeric excess (82%). The preference for a *syn* configuration contrasted with the *anti* predominance observed up to this point, so we pursued studies using these conditions.



Scheme 1

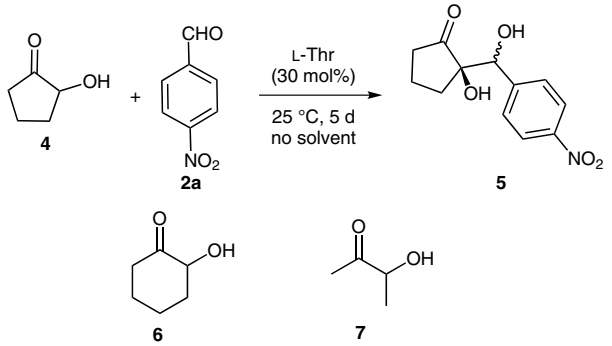
The next series of experiments (Table 1, entries 4–8) explored the generality of the reaction with regard to the aldehyde partner. After 48 hours of reaction with **1** in the presence of 20 mol% L-Thr, benzaldehydes bearing electron-withdrawing groups (**2b–e**) gave exploitable yields (upwards of 50%) of the corresponding aldol adducts **3b–e**). The *syn* diastereoselectivity trend remained, with diastereomeric ratios averaging around 4:1, and in most cases the enantioselectivity of the *syn* adduct was significant, with an enantiomeric excess ranging from 54% to 84%. On the other hand, benzaldehyde (**2f**) was unreactive over a period of 48 hours under the same conditions.

Table 1 Solvent-Free Direct Asymmetric Aldol Reaction of 2-Hydroxy Ketones **1** with Various Aldehydes **2** Catalyzed by L-Threonine[a]

Entry	α-Hydroxy ketone	Aldehyde	Product[13]	Time (h)	Yield (%)[b]	dr *syn*/*anti* (%)[13]	ee *syn* (%)[13]	ee *anti* (%)[13]
1[c]	**1**	**2a**	**3a**	170	25	23:77	60	38
2[d]	**1**	**2a**	**3a**	6	70	40:60	81	36
3	**1**	**2a**	**3a**	24	72	61:39	82	56
4	**1**	**2b**	**3b**	48	50	85:15	82	n.d.
5	**1**	**2c**	**3c**	48	50	84:16	72	48
6	**1**	**2d**	**3d**	48	60	70:30	84	n.d.
7	**1**	**2e**	**3e**	48	64	78:22	54	52
8	**1**	**2f**	–	48	0	–	–	–
9[e]	**4**	**2a**	**5**	120	53	69:31[f]	70[f]	48[f]
10[e]	**6**	**2a**	–	120	0	–	–	–
11[e]	**7**	**2a**	–	120	0	–	–	–

[a] Reactions conditions (unless otherwise indicated): α-hydroxy ketone (1.25 mmol), aldehyde (0.25 mmol), and L-Thr (0.05 mmol) stirred at 0–5 °C.
[b] Isolated product yields are given.
[c] Reagents dissolved in DMF (0.5 mL) and H_2O (2 mmol).
[d] Reaction carried out at 25 °C.
[e] Reaction conditions: α-hydroxy ketone (0.75 mmol), aldehyde (0.25 mmol), and L-Thr (0.075 mmol) stirred at 25 °C.
[f] The *syn* and *anti* isomers could not be unambiguously assigned.

The final series of experiments with related hydroxy ketone substrates (Table 1, entries 9–11) revealed the particular importance of the cyclobutane ring as the electrophile-supporting manifold. The solvent-free reaction of **2a** with 2-hydroxycyclopentanone (**4**) in the presence of 30 mol% L-Thr required five days at room temperature in order to attain >50% yield of the adduct **5**; this compound was obtained as an *syn*/*anti* mixture (69:31) with an enantiomeric excess of 70% for the major stereoisomer (Scheme 2). Significantly, under the same conditions, two other α-hydroxy ketones (**6** and **7**) gave no detectable aldol adducts after five days.



Scheme 2

Collectively, these results show that 2-hydroxycyclobutanone **1** is particularly amenable to solvent-free L-Thr-catalyzed direct aldol reactions with reasonable stereocontrol. The prevalence of a *syn* selectivity is consistent with Barbas' transition-state model for L-proline-catalyzed aldol reactions of α-hydroxyacetone,[10] in which the aldehyde's approach to the enamine is assisted by the carboxylic acid function in such a way that the aryl moiety is in the least sterically hindered orientation (Figure 1). The alcohol function on the Thr side chain may help to locate the water molecule for return during enamine hydrolysis. The *R* configuration at the quaternary chiral center is assumed by analogy with previous observations on product **3a** obtained in a solution-state aldol reaction.[5]

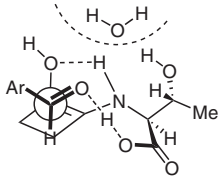


Figure 1 Plausible transition-state model for the aldol reaction

The work described here offers an alternative to the use of 1,2-bis(trimethylsilyloxy)cyclobutene to access Cα-quaternized derivatives of the title compound **1**,[11] while the 2-oxy-2-alkylcyclobutane molecular fragment is useful for diverse chemical transformations.[12] Development of this deracemizing 'green chemistry' approach to highly functionalized derivatives of **1** and further synthetic exploitation thereof should be facilitated.

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(13) A mixture of aldehyde (0.25 mmol), α-hydroxy ketone (1.25 mmol), and L-threonine (0.075 mmol) was stirred at 0–5 °C for the requisite time. The mixture was diluted with EtOAc and washed with half-sat. NH_4Cl solution. The water phase was further extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified by column chromatography (PE–Et_2O = 1:1) to afford the desired aldol product as an inseparable *syn*/*anti* mixture. The dr was determined by GC analysis. For ee determination, chiral HPLC analysis was used. When indicated, the aldol was first converted into the corresponding acetylated products[14] in effectively quantitative yield, to facilitated signal separation.

2-Hydroxy-2-[hydroxy(4-nitrophenyl)methyl]-cyclobutanone (3a)

This product was described previously.[5]

2-[(4-Fluorophenyl)(hydroxy)methyl]-2-hydroxycyclobutanone (3b)

Data obtained for a *syn*/*anti* mixture (85:15); white solid. IR (nujol): 3455, 1701 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 1.40–1.80 (m, 1 H, *syn*), 2.11–2.32 (dd, 1 H, *J* = 9.7, 10.7 Hz, *anti*), 2.31–2.51 (m, 3 H, *syn* + *anti*), 3.55–2.75 (m, 3 H, *syn* + *anti*), 4.57 (d, 1 H, *J* = 3.75 Hz, *syn*), 4.72 (br s, 1 H, *anti*), 5.72 (s, 1 H, *syn*), 5.94 (m, 1 H, *anti*), 6.40–6.51 (m, 2 H, *syn* + *anti*), 7.00–7.09 (m, 2 H, *syn* + *anti*), 7.25–7.38 (m, 2 H, *syn* + *anti*). ^{13}C NMR (62 MHz, DMSO-d_6): δ = 23.3 (*anti*), 25.7 (*syn*), 38.7 (*syn*), 41.4 (*anti*), 72.5 (*anti*), 74.8 (*syn*), 94.5 (*syn*), 95.1 (*anti*), 114.8 (*syn*), 115.1 (*anti*), 129.9 (*syn*), 130.1 (*anti*), 130.3 (*syn*), 130.4 (*anti*), 138.3 (*anti*), 138.6 (*syn*), 212.3 (*syn*), 214.7 (*anti*). EI-MS: *m/z* (%) = 192 (66) [M^+ – 18], 149 (15), 136 (69), 122 (100), 97 (50), 94 (54), 77 (22), 58 (28). After acetylation, the *ee* was determined using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 93:7, flow rate 1.1 mL/min, λ = 254 nm): t_R (*syn*) = 15.3 min (major), t_R (*syn*) = 17.4 min (minor).

2-{[4-(Trifluoromethyl)phenyl](hydroxy)methyl}-2-hydroxycyclobutanone (3c)

Data obtained for a *syn*/*anti* mixture (84:16); white solid. IR (nujol): 3470, 1703 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 1.41–1.58 (m, 1 H, *syn*), 1.58–1.79 (m, 1 H, *anti*), 2.08–2.42 (m, 4 H, *syn* + *anti*), 2.50–2.80 (m, 2 H, *syn* + *anti*), 4.63 (d, 2 H, *J* = 4.75 Hz, *syn* + *anti*), 5.87 (d, 2 H, *J* = 4.75 Hz, *syn* + *anti*), 6.02 (s, 1 H, *anti*), 6.08 (s, 1 H, *syn*), 7.28–7.62 (m, 8 H, *syn* + *anti*). ^{13}C NMR (62 MHz, DMSO-d_6): δ = 23.4 (*anti*), 26.2 (*syn*), 38.7 (*anti*), 42.2 (*syn*), 72.7 (*syn*), 75.2 (*anti*), 94.4 (*syn*), 94.8 (*anti*), 123.3 (*anti*), 125.1 (*syn*), 125.3 (*anti*), 127.6 (*anti*), 128.4 (*syn*), 129.0 (*syn* + *anti*), 129.4 (*syn*), 147.2 (*syn* + *anti*), 212.1 (*syn*), 214.3 (*anti*). EI-MS: *m/z* (%): 242 (47) [M^+ – 18], 186 (63), 173 (61), 172 (100), 145 (80), 127 (59), 58 (30). After acetylation, the ee was determined using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 98:2, flow rate 1 mL/min, λ = 254 nm): t_R (major) = 28 min (*syn*), t_R (minor) = 38 min (*syn*); t_R (minor) = 26 min (*anti*), t_R (major) = 49.7 min (*anti*).

2-[(2,4-Dichlorophenyl)(hydroxy)methyl]-2-hydroxycyclobutanone (3d)

Spectral data worked out from the *syn*/*anti* mixture (70:30); white solid. IR (KBr): 3479, 1723 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 1.69 (q, 1 H, *J* = 10. 5 Hz, *syn*), 1.82 (q, 1 H, *J* = 10. 4 Hz, *anti*), 2.30 (dq, 1 H, *J* = 5.0, 11.3 Hz, *anti*), 2.51 (q, 1 H, *J* = 11.3 Hz, *syn*), 2.66–2.80 (m, 4 H, *syn* + *anti*), 5.02 (d, 1 H, *J* = 4.00 Hz, *syn*), 5.05 (d, 1 H, *J* = 3.3 Hz, *anti*), 5.87 (d, 1 H, *J* = 4.75 Hz, *syn*), 6.02 (s, 3 H, *syn* + *anti*), 7.34–7.61 (m, 6 H, *syn* + *anti*). ^{13}C NMR (62 MHz, DMSO-d_6): δ = 23.7 (*anti*), 25.4 (*syn*), 40.3 (*syn*), 40.8 (*anti*), 68.2 (*anti*), 70.1 (*syn*), 94.1 (*anti*), 94.2 (*syn*), 126.7 (*syn* + *anti*), 127.8 (*syn*), 127.9 (*anti*), 131.0(*anti*), 131.2 (*syn*), 132.3 (*syn* + a*nti*), 133.2 (*anti*), 133.4 (*syn*), 138.2 (*syn*), 138.3 (*anti*), 210.8 (*syn*), 211.4 (*anti*). EI-MS: *m/z* (%) = 242 (36) [M^+ – 18], 186 (59), 174 (80), 172 (100), 111 (49), 75 (27). After acetylation, the ee was determined using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH = 98:2, flow rate 1 mL/min, λ = 254 nm): t_R (major) = 8.9 min (*syn*), t_R (minor) = 11.6 min (*syn*).

4-[Hydroxy-(1-hydroxy-2-oxo-cyclobutyl)-methyl]benzonitrile (3e)

Data obtained for a *syn*/*anti* mixture (78:22); colorless oil. IR (neat): 3388, 2236, 1941, 1785 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.76–1.84 (m, 1 H, *anti*), 1.92 (q, 1 H, *J* = 11.0 Hz, *syn*), 1.98–2.07 (m, 1 H, *syn*), 2.08–2.17 (m, 1 H, *anti*), 2.27 (dt, 1 H, *J* = 5.0, 12.0 Hz, *syn*), 2.35 (dt, 1 H, *J* = 5.0, 12.5 Hz, *anti*), 2.38–2.84 (m, 4 H, *syn* + *anti*), 4.20–4.80 (m, 2 H, *syn* + *anti*), 4.90 (s, 2 H, *syn* + *anti*), 7.49–7.62 (m, 8 H,

syn + *anti*). ^{13}C NMR (124 MHz, $CDCl_3$): δ = 21.3 (*anti*), 23.2 (*syn*), 41.2 (*syn*), 41.7 (*anti*), 73.9 (*syn*), 81.6 (*anti*), 93.4 (*syn* + *anti*), 111.8 (*syn* + *anti*), 118.4 (*syn* + *anti*), 127.8 (*anti*), 128.0(*syn*), 132.0(*anti*), 132.1 (*syn*), 143.4 (*syn*), 144.2 (*anti*), 210.4 (*syn*), 211.4 (*anti*). EI-MS: *m/z* (%) = 199 (27) [M^+ – 18], 143 (37), 130 (48), 129 (56), 115 (21), 102 (29), 77 (14), 40 (100). The ee was determined using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 39.9 min (*syn*), t_R (minor) = 25.9 min (*syn*); t_R (minor) = 27.8 min (*anti*), t_R (major) = 32.8 min (*anti*).

2-Hydroxy-2-[hydroxy(4-nitrophenyl)methyl]-cyclopentanone (5)

Data obtained for a *syn*/*anti* mixture (69:31), obtained using the modified conditions stated in Table 1 (footnote f); orange oil. IR (neat): 3422, 1750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–2.43 (m, 12 H), 4.87 (s, 1 H), 4.93 (s, 1 H), 7.53–7.57 (m, 4 H), 8.19–8.22 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 29.6, 30.8, 32.1, 36.1, 37.2, 74.7, 74.8, 79.1, 79.7, 104.1, 104.8, 123.1, 123.3, 128.0, 145.0, 147.0, 216.4, 217.1. EI-MS: *m/z* (%) = 234 (1) [M^+ – 17], 165 (10), 150 (10), 100 (100), 77 (30), 55 (16), 43 (16). The ee was determined using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH = 92:8, flow rate 0.8 mL/min, λ = 254 nm): t_R (major) = 24.1 min (*syn*), t_R (minor) = 25.0 min (*syn*); t_R (major) = 21.8 min (*anti*), t_R (minor) = 36.7 min (*anti*).

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