Aldol Reactions in Water Using a β-Cyclodextrin-Binding Proline Derivative

Kegang Liu, Daniel Häussinger, Wolf-D. Woggon*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland
Fax +41(61)2671102; E-mail: wolf-d.woggon@unibas.ch

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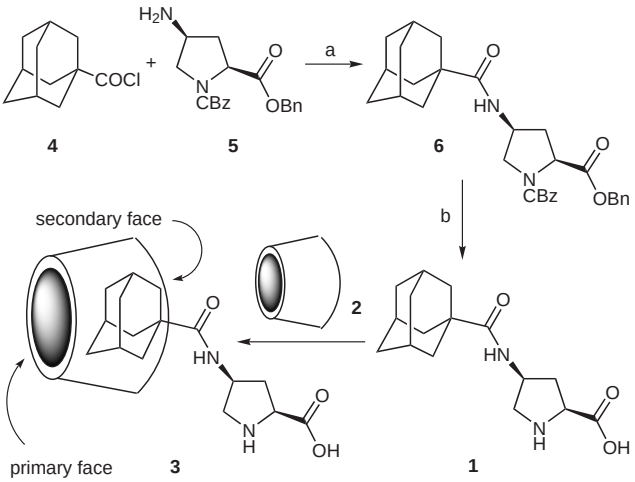
Abstract: The aldol reaction of various aromatic aldehydes with cyclohexanone is catalyzed by the inclusion complex of a proline derivative and β-cyclodextrin in water, yielding hydroxyketones with *anti*/*syn* ratio of up to 99:1 and ee values well above 90%.

Key words: adamantane, aldol reaction, β-cyclodextrin, proline, organocatalysis

Enantioselective organocatalysis[1] has experienced a renaissance in catalytic asymmetric reactions, especially for the aldol reaction, one of the most efficient carbon–carbon bond-forming reactions in organic synthesis.[2] Several asymmetrical methodologies for this reaction using organocatalysts have been developed,[3] but most of the reactions are pursued in organic solvents, such as DMSO, DMF, or $CHCl_3$. In contrast, enzymes and antibodies can catalyze aldol reactions in water,[4,5] but substrate scope limits their practical application. Recently, some research groups reported highly diastereo- and enantioselective aldol reactions in water,[6] using for example amphiphilic dendritic catalysts and polystyrene-supported proline derivatives [6d,e] and hence it has been debated whether the term 'in water' is justified.[7] Herein, we describe the synthesis and application of a simple proline derivative which forms inclusion complexes with β-cyclodextrin and hence is completely soluble in water catalyzing aldol reations under neutral conditions with high diastereo- and enantioselectivity.

The concept involves the attachment of an adamantyl subunit to proline, see **1**. The target structure **1** was conveniently prepared in two steps from commercially available **4** and **5**[8] and subsequent hydrogenolysis of **6**.[9,10] According to ^{1}H NMR spectroscopy the adamantane amide **1** binds to β-cyclodextrin **2** yielding the 1:1 complex **3** (Scheme 1).[11] A characteristic upfield shift of the triplet of H at C3′ (3.94 ppm) of the glucose unit indicates the inclusion of the adamantane into the cavity of **2**. NMR-controlled titration of β-cyclodextrin **2** with aliquots of the organocatalyst **1** led to a continuous shift of this triplet from which the binding constant $K_{ass} = 1.4 \cdot 10^4$ mol^{-1} was determined.[12]

The orientation of the adamantane unit as shown in Scheme 1 was deduced from the NOSY spectrum of **3** (Figure 1).The significant cross peaks indicate the



Scheme 1 Synthesis and structure of organocatalyst **1** and its β-cyclodextrin inclusion complex **3**. *Reagents and conditions*: a) DIPEA, CH_2Cl_2, r.t., 93%; b) H_2, 10%Pd/C, MeOH, 100%.

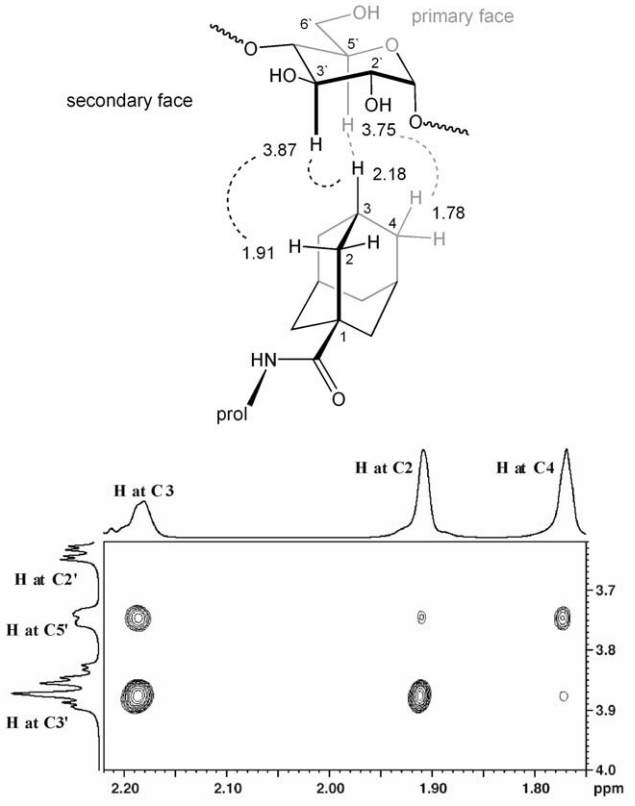


Figure 1 The orientation of **1** within the cavity of β-cyclodextrin **2**; ^{1}H shifts and NOE contacts between **1** and **2** are indicated in the cartoon above. Region of the NOESY spectrum of an equimolar mixture of **1** and **2** (D_2O, 298 K, 600 MHz) is shown below.

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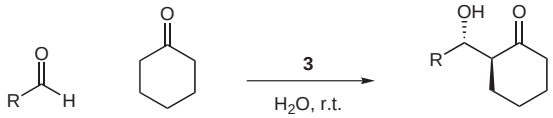
proximity of H at C-3′ of glucose to H at C2 of adamantane and the interaction of H at C5′ and H at C4. The proton at C-3 of adamantane is close to both protons at C3′ and at C5′ of glucose. It follows that the adamantane amide protrudes beyond the secondary face of β-cyclodextrin.[13]

A representative set of aldehydes was examined in detail using catalyst **3** and cyclohexanone. The reactions proceeded smoothly in excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to >99% ee) to furnish the aldol adducts **9a**–**n**, see Table 1.[14,15]

The reactions of cyclohexanone **8** with benzaldehydes bearing electron-withdrawing groups (entries 1–8) gave moderate to excellent yields (48–97%). In contrast, the yields of the reactions with *p*-tolylaldehyde **7j** and 1-naphthaldehyde **7k** were somewhat lower (entries 10 and 11). Interestingly, the reactions of **8** with the pyridine aldehydes **7m** and **7n** (entries 13 and 14), were very fast and high yields were observed, but the distereoselectivities were disappointingly low. However, except for one case (entry 14), the enantioselectivities are well above 90%ee. A further advantage of the system is the facile recovery of the catalyst. After completion of the reaction and subsequent extraction of the product with dichloromethane the catalyst remaining in the aqueous layer can be reused in subsequent reactions, entries 15–17 show that **3** can be recycled up to four times without changes in reactivity and enantioselectivity.

In conlusion, the easy access and recycling of the catalyst and the high enantio- and diastereoselectivity of the reaction makes this procedure an attractive alternative to existing methods [6] for the synthesis of β-hydroxy ketones in water.

Table 1 Asymmetric Aldol Reaction in Water Catalyzed by **3**



7 **8** **9**

Entry	R[a]	Product	Time (h)	Yield (%)[b]	*anti*/*syn*[c]	ee (%, *anti*)[d]
1	**7a** 4-$NO_2C_6H_4$	**9a**	72	88	90:10	91
2	**7b** 2-$NO_2C_6H_4$	**9b**	72	80	96:4	96
3	**7c** 4-$CF_3C_6H_4$	**9c**	72	94	92:8	99
4	**7d** 4-NCC_6H_4	**9d**	72	90	90:10	94
5	**7e** 4-ClC_6H_4	**9e**	72	48	92:8	98
6	**7f** 2-ClC_6H_4	**9f**	72	84	94:6	>99
7	**7g** 4-FC_6H_4	**9g**	96	60	87:13	97
8	**7h** 2,6-diClC_6H_3	**9h**	48	97	>99:1	97
9	**7i** Ph	**9i**	72	50	92:8	97
10	**7j** 4-MeC_6H_4	**9j**	96	28	86:14	95
11	**7k** 1-Naphthyl	**9k**	96	31	92:8	94
12	**7l** 2-Furyl	**9l**	72	62	81:19	96
13	**7m** 2-Pyridyl	**9m**	3	98	60:40	92
14	**7n** 4-Pyridyl	**9n**	3	90	69:31	39
15	**7c** 2nd Cycle	**9c**	80	86	92:8	99
16	**7c** 3rd Cycle	**9c**	72	90	92:8	99
17	**7c** 4th Cycle	**9c**	72	92	92:8	99

[a] The reaction was performed with aldehyde **7** (0.2 mmol), ketone **8** (0.8 mmol), **3** (0.02 mmol), and H_2O (0.2 mL) at r.t.
[b] Combined yields of isolated diastereoisomers.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral-phase HPLC of the *anti* product.

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(9) **Synthesis of 6**
To a solution of **5** (70.8 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added solid 1-adamantane carboxylic acid chloride **4** (44 mg, 0.22 mmol) at 0 °C, followed by addition of DIPEA (52 mg, 0.4 mmol). The reaction mixture was stirred for 4 h at r.t. and finally diluted with CH_2Cl_2 (5 mL). The organic phase was washed consecutively with 1 N HCl, H_2O, brine and dried over Na_2SO_4.The solvent was removed under reduced pressure. Purification of the residue by flash chromatography using hexane–EtOAc (2:1) affords **6** as an oil (96 mg, 93%); $[\alpha]_D^{25}$ –32.1 (*c* 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.37 (m, 10 H), 6.65 (d, 1 H, *J* = 9.2 Hz), 4.95–5.34 (m, 4 H), 4.69 (m, 1 H), 4.41–4.50 (m, 1 H), 3.51–3.71 (m, 2 H), 2.41–2.50 (m, 1 H), 2.00 (m, 3 H), 1.91 (m, 1 H), 1.63–1.73 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.86, 177.78, 174.45, 155.16, 154.52, 136.65, 136.57, 135.68, 135.44, 129.06, 128.98, 128.94, 128.89, 128.57, 128.52, 128.44, 128.38, 128.23, 67.82, 67.73, 58.66, 58.20, 54.41, 54.12, 48.70, 47.72, 40.87, 40.86, 39.27, 39.26, 37.39, 36.87, 36.32, 28.47. ESI-MS: *m/z* = 539.2 $[M + Na]^+$, 555.1 $[M + K]^+$. Anal. Calcd (%) for $C_{31}H_{36}N_2O_5$: C, 72.07; H, 7.02; N, 5.42. Found: C, 71.27; H, 7.09; N, 5.20.

(10) **Synthesis of 1**
To a solution of compound **6** (96 mg, 0.186 mmol) in MeOH (2 mL) was added 10% Pd/C (30 mg). The reaction mixture was stirred for 5 h under hydrogen, subsequently filtered through Celite and the catalyst was washed with MeOH three times. The combined organic solutions were concentrated under reduced pressure to afford the proline derivative **1** as a colorless solid (54 mg, 100%); mp 230–232 °C; $[\alpha]_D^{25}$ –32.9 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.60 (d, 1 H, *J* = 6.8 Hz), 4.34 (m, 1 H), 4.15 (t, 1 H, *J* = 8.4 Hz), 3.28 (dd, 1 H, *J* = 11.2, 7.2 Hz), 3.10 (dd, 1 H, *J* = 11.2, 6.0 Hz), 2.46 (m, 1 H), 1.91 (m, 4 H), 1.58–1.72 (m, 12 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.93, 170.99, 58.99, 49.98, 48.50, 39.30, 36.94, 34.67, 28.43. ESI-MS: *m/z* = 293.4 $[M + 1]^+$. Anal. Calcd (%) for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.66; H, 8.18; N, 9.44.

(11) **Spectroscopic Data of Inclusion Complex 3**
^{1}H NMR (600 MHz, D_2O): δ = 5.04 (d, 7 H, H-1′), 4.55 (m, 1 H, H-γ), 4.22 (dd, 1 H, H-α), 3.89 (m, 7 H, H-6″), 3.87 (m, 7 H, H-3′), 3.84 (m, 7 H, H-6′), 3.75 (m, 7 H, H-5′), 3.64 (dd, 7 H, H-2′), 3.60 (dd, 1 H, H-δ *cis*), 3.56 (dd, 7 H, H-4′), 3.46 (dd, 1 H, H-δ *trans*), 2.66 (m, 1 H, H-β *cis*), 2.20 (m, 1 H, H-β *trans* to Hα), 2.18 (s, 3 H, H-3), 1.91 (s, 6 H, H-2), 1.78 (s, 6 H, H-4). ^{1}H NMR (600 MHz, H_2O): δ = 7.37 (d, 1 H, NHC=O). ^{13}C NMR (151 MHz, D_2O): δ = 180.7 (NHC=O), 174.3 (COOH), 102.7 (C-1′), 81.9 (C-4′), 73.5 (C-3′), 72.4 (C-2′), 72.3 (C-5′), 60.6 (C-α), 60.5 (C-6′), 50.4 (C-δ), 49.2 (C-γ), 40.9 (C-1), 38.9 (C-2), 36.8 (C-4), 34.8 (C-β), 27.8 (C-3).

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(13) The NOESY spectrum was acquired on an equimolar mixture of **1** and **2** in D_2O using a mixing time of 500 ms and 512 (142 ms) and 2048 (285 ms) points (acquisition times) in the F1 and the F2 dimension. Assignment of the resonances of this complex was accomplished using standard COSY, HMQC, and HMBC pulse sequences. NMR data were processed using Bruker XWINNMR software.

(14) **General Procedure for the Aldol Reaction Catalyzed by the Inclusion Complex of 1 and β-Cyclodextrin 2**
To a suspension of the proline derivative **1** (5.84 mg, 0.02 mmol) in H_2O (0.2 mL) was added β-cyclodextrin **2** (22.7 mg, 0.02 mmol) and stirred for 10 min at r.t. until a clear solution was obtained; then cyclohexanone (80 μL, 0.8 mmol) was added. The reaction mixture was stirred at r.t. for further 10 min and subsequently aldehyde **7** (0.2 mol) was added. The reaction mixture was stirred for 3–96 h (TLC monitoring the consumption of aldehyde). The reaction was quenched with aq NH_4Cl and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4. Purification by flash chromatography (silica gel, hexane–EtOAc, 2:1) gave the pure aldol products for further analysis.
For Recycle Case
After the completion of reaction, the reaction mixture was directly extracted with CH_2Cl_2 for three times. The aqueous-phase-containing catalyst was reused again for next time after removing a little amount of CH_2Cl_2 under reduced pressure.

(15) Absolute configuration of the aldol products *anti*-**9** were determined by optical rotation in comparison to reported values[6] except compound **9h**.
The following are the analytical data of 2-hydroxy-methylene-(2′,6′-dichlorophenyl) cyclohexanone (**9h**):
anti-**9h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 7.13 (m, 1 H), 5.82 (dd, 1 H, *J* = 9.6, 4.4 Hz), 3.67 (d, 1 H, *J* = 4.4 Hz), 3.46–3.49 (m, 1 H), 2.35–2.52 (m, 2 H), 2.05–2.09 (m, 1 H), 1.78–1.82 (m, 1 H), 1.62–1.69 (m, 2 H), 1.49–1.53 (m, 1 H), 1.34–1.41 (m, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.85, 136.08, 135.10, 129.92, 70.97, 54.04, 42.85, 30.26, 28.04, 25.10. ESI-MS: *m/z* (%) = 295.3 (100) $[M + Na]^+$. The ee of *anti*-**9h** (97%) was determined by HPLC with a Chiralpak AD-H column (heptane–2-PrOH, 90:10), 20 °C, 210 nm, 0.5 mL/min; major enantiomer t_R = 24.2 min, minor enantiomer t_R = 30.9 min.
syn-**9h**: ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.08–7.31 (m, 3 H), 5.73 (t, 1 H, *J* = 7.6 Hz), 3.27–3.33 (m, 1 H), 2.84 (d, 1 H, *J* = 7.6 Hz), 1.17–2.40 (m, 8 H). The ee was determined by HPLC with a Chiralpak AD-H column (heptane–2-PrOH, 90:10), 20 °C, 210 nm, 0.5 mL/min, one enantiomer t_R = 20.2 min, another enantiomer t_R = 22.1 min.