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Hydrophobic Substituent Effects on Proline Catalysis of Aldol Reactions in Water

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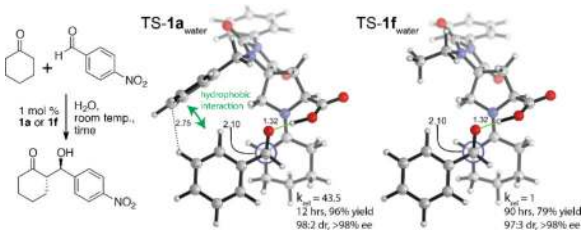
Abstract



Derivatives of 4-hydroxyproline with a series of hydrophobic groups in well-defined orientations have been tested as catalysts for the aldol reactions. All of the modified proline catalysts carry out the intermolecular aldol reaction in water and provide high diastereoselectivity and enantioselectivity. Modified prolines with aromatic groups *syn* to the carboxylic acid are better catalysts than those with small hydrophobic groups (**1a** is 43.5 times faster than **1f**). Quantum mechanical calculations provide transition structures, TS-**1a**$_{water}$ and TS-**1f**$_{water}$ that support the hypothesis that a stabilizing hydrophobic interaction occurs with **1a**.

Introduction

In the past decades, small, metal-free organic molecules have attracted considerable attention as asymmetric organocatalysts.[1] Despite considerable effort, the vast majority of organocatalysts carry out relatively few turnovers; typically more than 10 mol % of catalyst is necessary to achieve reasonable reaction rates and yields. X-ray structures of highly active enzymes show intricate active sites that have shape and chemical complementarity to their substrates and they suggest the hypothesis that the activity of organocatalysts might be improved by creating specific interactions between the organocatalyst and their substrates. In non-aqueous solvents, organocatalysts must utilize specific hydrogen bonding, charge-charge and dipole-charge interactions to drive the association of the organocatalyst with their substrates.[2] In water, on the other hand, organocatalysts need to make use of the hydrophobic interaction because the high dielectric constant of water screens charge-charge interactions and water competes for hydrogen bonds. The development of organocatalytic

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Supporting Information Available: Experimental procedures and characterization of catalysts, aldol reactions and catalyst recycling, full citation for ref. 16, energies and Cartesian coordinates for all computed structures. These are available free of charge via the Internet at http://pubs.acs.org.

asymmetric reactions in aqueous media is an attractive goal because water is an inexhaustable and environmentally friendly solvent.[3,4]

Proline was found, in the 1970s, by Hajos and Parrish[5] and Eder, Sauer and Wiechert[6] to be an organocatalyst for the intramolecular aldol reaction and, in 2000, by List, Lerner and Barbas to be an organocatalyst for the intermolecular aldol reaction.[7] In organic solvents, proline requires high loadings (~ 30 mol %) and it is well known that proline does not catalyze the aldol reaction in water.[8] Since the initial reports of the proline-catalyzed aldol reaction, derivatives of 4-hydroxyproline have attracted considerable interest as catalysts of the asymmetric aldol reaction in water. [9] In these previous reports, hydrophobic substituents were attached to the alcohol of 4-hydroxyproline and cyclic ketones were combined with aldehydes and catalyst in an aqueous, biphasic environment formed by the mixture of water and the organic ketone. The organic ketone and the modified proline catalyst have been proposed to assemble into micelles in water due to hydrophobic interactions, excluding water and driving the formation of the enamine.[8] The enamine is then more soluble in the organic phase where it reacts with the aldehyde to form the carbon-carbon bond and then hydrolysis of the resulting iminium ion takes place. In contrast to this phase-transfer type of mechanism, we explore here the idea that precisely placed hydrophobic groups on modified prolines could create specific hydrophobic interactions with the aldol substrates in water to create organocatalysts that have high activity as well as high diastereo- and enantio-selectivity.

Recently, we have begun exploring the creation of catalytic sites through the rational organization of functional groups on bis-peptide scaffolds. Bis-amino acids are cyclic, stereochemically pure building blocks derived from (2*S*,4*R*)-4-hydroxyproline that are combined with other bis-amino acids and α-amino acids through functionalized diketopiperazines to create spiro-ladder oligomers with programmable shape and functionality.[10] Our experience in synthesizing richly functionalized prolines led to the idea of positioning hydrophobic groups that could interact with the substrates of proline aldol catalysis in order to improve diastereoselectivity, enantioselectivity and turnover rate. Herein, we report a series of modified prolines that exhibit excellent diastereoselectivity and enantioselectivity with very low loading (0.5 mol%) in an aldol reaction in water. Moreover, by placing appropriate hydrophobic groups either syn or anti to the carboxylic acid of proline, we demonstrate a structure/catalytic activity relationship together with computational modeling that suggests that a specific hydrophobic interaction between the catalyst and the aldehyde substrate is responsible for an observed rate enhancement of 43.5-fold when compared to a catalyst that cannot form a hydrophobic interaction.

Results and Discussion

Modified proline **1a** was synthesized starting from (2*S*,4*R*)-4-hydroxyproline **4** in eight steps with an overall yield of 44% (Scheme 1). Our group previously described the first five steps in the synthesis of **5, 6** and their enantiomers.[10] The free amine of **5** was reductively alkylated overnight using benzaldehyde and sodium cyanoborohydride in methanol at room temperature. The resulting *N*-carboxybenzyl amino acid **7** was combined with 1.05 equiv. phenylisocyanate and 3 equiv. Et_3N at room temperature and stirred overnight. The hydantoin **12** formed cleanly with spontaneous dehydration; the formation of these tetrasubstituted hydantoins is facile under these mild conditions due to assistance by the Thorpe-Ingold effect and the presence of *N*-alkyl substitution on the amino acid.[11] The carboxybenzyl and *tert*-butyl protecting groups were then removed with 33% HBr in acetic acid and the HBr salt was converted to the TFA salt **1a**. Using this reaction sequence starting from **5** and a variety of aldehydes in place of benzaldehyde afforded organocatalysts **1b–1e**. Catalysts **2a** and **2b**, which are epimeric to **1a** and **1b** at the spiro carbon on the pyrrolidine

ring, were prepared analogously starting from **6** (the C4 epimer of **5**) and the appropriate aldehyde. Catalysts **1f** and **2c** were synthesized using similar procedures to **1a–1e, 2a** and **2b** but no intermediates were isolated. Finally, the organocatalyst **3** was prepared by converting the amino acid **7** to the 1-hydroxy-7-azabenzotriazole (HOAt) ester (not isolated) and combining it with the *N*-functionalized amino-isobutyric acid **22** to form the hexa-substituted diketopiperazine **17** using a new reaction that we have previously described called "acyl-transfer coupling".[10b] The carboxylbenzyl amine and *tert*-butyl ester of **17** were deblocked using HBr/AcOH and the salt was then converted to the trifluoroacetate salt **3**.

To probe the catalytic activity of **1a** in the aldol reaction, **1a** (10 mol %) was combined with 1 equiv. 4-nitrobenzaldehyde and 10 equiv. cyclohexanone at room temperature in a variety of solvents (Table 1). Solvent screening indicated that water and methanol afford the highest diastereomeric ratios and enantioselectivities (entries 1 and 2, the values are capped at 98% given the practical limits of quantitation by NMR).[12] The reaction catalyzed by **1a** was found to be considerably faster in water than in methanol, as the consumption of the starting *para*-nitrobenzaldehyde remained incomplete in the latter solvent after 12 hours.

The scope of aldol catalysis using **1a** in water against a variety of aldehydes and ketones as substrates is shown in Table 2. Generally, the reaction between cyclohexanone and aldehydes with an electron-withdrawing substituent was found to proceed to completion with high yield and excellent diastereoselectivity and enantioselectivity (entries 1, 4, 5, 6, and 10). The reaction of cyclohexanone and *para*-nitrobenzaldehyde catalyzed by **1a** (0.5 mol %) provided the aldol product in 96% yield within 78 hours (entry 11). Substituted benzaldehydes containing less electron-withdrawing groups required longer reaction times to achieve good isolated yields, but the diastereo- and enantioselectivities remain excellent (entries 7 and 8). The methoxy-substituted aldehyde (electron-donating) showed poor conversion and slightly lower diastereoselectivity but excellent enantioselectivity was maintained (>98%, entry 9). The reactivity of **1a** with cyclopentanone is good (entry 2: 9 hours, 98% yield) with a slight reduction in diastereoselectivity but excellent enantioselectivity. This is noteworthy, considering that there are few reports of catalyzed aldol reactions of cyclopentanone with high levels of diastereo- and enantioselectivity.[9c, 9i, 9h, 13] Cycloheptanone required 10 mol % loading of **1a** to achieve a yield of 77% in 48 hours (entry 3). The diastereoselectivity was modest (*anti / syn* = 1 : 4) but the enantioselectivity of the major, *anti* product was good (94% ee).

Catalyst **1a** can be recycled, due to its good solubility in water (Table 3), by extracting the completed reaction mixture with hexanes and then adding fresh substrate to the aqueous layer. The high diastereoselectivity and enantioselectivity were maintained through three cycles with an approximately 50% decrease in activity, possibly due to the loss of some catalyst as it partitioned into the organic phase.

To probe the relationship between catalyst structure and activity, a series of derivatives **1a–1f, 2a–2c**, and **3** (Scheme 1), which bear different aromatic groups varying stereochemistry and ring structures at the quaternary carbon, was synthesized. To a first approximation, the activities and selectivities of catalysts **1b–1e** are indistinguishable from those of **1a**. Switching from the **1a–1b** catalysts to the corresponding **2a–2b** catalysts involves inverting the C-4 stereocenter, which flips the aromatic side-arm to the opposite side of the proline ring (anti to the carboxylic acid) and leads to a large drop in catalyst rate, requiring over 7 times longer to achieve yields comparable to those of **1a–1b** (Table 4). When the benzyl substituent on the hydantoin of **1a** was changed to an ethyl group (catalyst **1f**), the activity of the catalyst drops to that of **2a** and **2b** coupled with a slight decrease in diastereoselectivity. Expanding the hydantoin on the quaternary center of **1a** to the diketopiperazine **3** (entry 8) demonstrates comparable activity to **1a** with a slight reduction in diastereoselectivity. These

observations are consistent with the formation of an additional hydrophobic interaction between the benzyl group on the hydantoin of **1a** or the similarly placed aromatic group on the hydantoin of **1b–1e** and **3** and the aldehyde substrate in the transition state. In toluene, the activity of **1a** is almost identical to that of **1f** and **2a**, which would be expected when the hydrophobic effect is eliminated.

To gain more precise measurements of the relative catalytic rates we selected three catalysts: **1a, 2a** and **1f** and measured the reaction kinetics of the catalyzed aldol reactions using the procedure described in the experimental section. The relative amounts of product and starting material at a series of time-points were measured using NMR and the data was fit to a first order kinetic model using non-linear optimization. The results demonstrated that catalyst **1a** reacts 43.5 times faster than **1f,** which has the same stereochemistry as **1a** but presents only an ethyl group and that **1a** is 9 times faster than catalyst **2a**, which is the C4-epimer of **1a** (Figure 1).

To better understand the nature of the reaction transition states, quantum chemical computations were performed on the aldol reactions of cyclohexanone and benzaldehyde using **1a** and **1f** (Table 5). The geometries were optimized by M06-2X/6-31G(d) in the gas phase and using the SMD model with water as solvent. [14] In vacuum, the difference in free energy of TS-**1a** and TS-**1f** is very small (0.2 kcal/mol) (Table 5). This is consistent with the very similar rates of **1a** and **1f** in toluene (entries 11 and 12 in Table 4). On the other hand, in water, the free energy of activation associated with **1a** is more stabilizing than **1f** by 2.6 kcal/mol (Table 5). The optimized transition states taking into account the solvation effect of water are illustrated in the Figure 2. The benzyl side-arm of **1a** comes into edge-to-face contact with the aromatic ring of the acceptor aldehyde in the List-Houk transition state, affording stabilization of TS-$\mathbf{1a}_{water}$ relative to TS-$\mathbf{1f}_{water}$. This is in excellent agreement with the experimentally observed 43.5-fold acceleration with the use of **1a** in water when compared with **1f**. Using transition state theory, the value of $\Delta\Delta G^{\ddagger}$ associated with a k_{rel} of 43.5 is −2.3 kcal/mol at 300 K. The SMD model treats solvent as a dielectric medium with a surface tension term calculated at the solute-solvent boundary that models the hydrophobic effect.[14] These results are consistent with the hypothesis that the observed acceleration is due to a hydrophobic interaction in **1a** that is not present in **1f**.[15]

In summary, we present a series of proline-based catalysts **1a–1e**, and **3** that catalyze the aldol reaction in water with high activity and excellent diastereo- and enantioselectivity. Both enantiomers of these catalysts are synthetically accessible starting from (2*S*,4*R*)-4-hydroxyproline[10] making them practical catalysts for the synthesis of stereochemically pure aldol products. Catalysts that present an aromatic group that can interact with the aromatic ring of the aldehyde acceptor through a specific hydrophobic interaction are significantly faster than those that do not. Quantum chemical calculations point to a hydrophobic edge-to-face interaction that stabilizes the transition state of **1a** relative to **1f** by 2.6 kcal/mol, in excellent agreement with the experimentally observed $\Delta\Delta G^{\ddagger}$ of 2.3 kcal/mol. These results suggest that the rational positioning of hydrophobic functional groups can significantly stabilize transition states through hydrophobic interactions in water and that stepwise incorporation of more groups could lead to proline aldol catalysts with even greater activity.

Experimental Section

General procedure for synthesis of catalyst 1a–1e, 2a and 2b

Step 1—To a solution of (3*S*,5*S*)-1-((benzyloxy)carbonyl)-5-(*tert*-butoxycarbonyl)-3-aminopyrrolidine-3-carboxylic acid **5** (2.0 g, 5.5 mmol, 1.0 eq) in methanol (60 mL), benzaldehyde (670 μL, 6.6 mmol, 1.2 eq) was added and stirred for 30 minutes at room

temperature. Sodium cyanoborohydride (518 mg, 8.3 mmol, 1.5 eq) was then added and stirred for 20 hours at room temperature until the reaction was complete, as monitored by LC-MS. The reaction mixture was concentrated under vacuum and the resulting residue was dissolved in 50 mL H_2O. The pH was adjusted to 7 by dropwise addition of 2 N HCl and the white precipitate (2.2 g, 4.8 mmol, 88% yield) was obtained by vacuum filtration. This product was used without further purification in the next step. For characterization, the compound was purified by reverse phase C_{18} high performance liquid chromatography using a 5–95% H_2O/Acetonitrile gradient.

(3*S*,5*S*)-3-(Benzylamino)-1-[(benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]pyrrolidine-3-carboxylic acid, 7: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K,δ): 1.38 (9H, s), 2.36 (1H, dd, J= 8.5, 13.3), 2.93 (1H, dd, J= 8.4, 13.3), 3.70 (1H, d, J= 11.4), 4.19 (3H, m), 4.34 (1H, t, J= 8.2), 5.11 (2H, s), 7.30–7.50 (10H, m); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 28.0, 28.2, 30.9, 49.0, 55.0, 59.4, 66.7, 81.2, 127.2, 127.8, 128.1, 128.5, 128.7, 137.3, 140.4, 154.2, 170.9, 174.4, 206.2; HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1% formic acid): T_r = 17.3 mins; HRMS-ESI: m/z Calculated for $C_{25}H_{31}N_2O_6$ $(M+H)^+$ 455.2177; Found: 455.2182.

Step 2—To a solution of **7** (2.2 g, 4.8 mmol, 1.0 eq), triethylamine (1.4 mL, 10.2 mmol, 2.1 eq) in 130 mL of anhydrous THF, phenyl isocyanate (1.1 mL, 9.7 mmol, 2.0 eq) was added in one portion. The reaction was stirred at room temperature for 20 hours until completion, as determined by LC-MS. The reaction was quenched with saturated NH_4Cl (aq.) (40 mL) and extracted with EtOAc (100 mL + 2x50 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The yellow, solid product was obtained by removal of the solvent in vacuum. The crude product **12** was used directly in the next step without further purification. For characterization, the compound was purified by reverse phase column using 5–95% H_2O/Acetonitrile gradient. Note: diphenyl urea was found in the crude product mixture (detected by LCMS), but it did not interfere with the next step.

7-Benzyl-8-*tert*-butyl(5*S*,8*S*)-1-benzyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 12: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.34 (9H, s), 2.21 (1H, dd, J= 8.3, 13.8), 2.72 (1H, dd, J=8.6, 13.7), 3.60 (1H, d, J= 11.8), 4.00 (1H, d, J= 11.8), 4.39 (1H, t, J= 8.4), 4.69 (2H, s), 5.10 (2H, s), 7.29–7.43 (11H, m), 7.50 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 298K, δ): 27.8, 36.3, 43.4, 50.3, 58.3, 66.3, 67.6, 82.1, 125.8, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 129.0, 129.1, 131.3, 136.0, 136.8, 154.1, 154.8, 170.8, 173.2; IR (neat): 1692, 1402, 1348, 1149, 1124 cm^{-1}; $[\alpha]_D^{18}$ = −5.0 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 26.3 mins; HRMS-ESI: m/z Calculated for $C_{32}H_{33}N_3NaO_6$ $(M+Na)^+$ 578.2262; Found: 578.2267.

Step 3—Ph-[Cbz, t-Bu] Pro4 (SS) hydantoin **12** (4.8 mmol) was dissolved in CH_2Cl_2 (20 mL) followed by the addition of 33% HBr/AcOH (40 mL). The reaction was stirred at room temperature for 2 hours. Removal of solvents by vacuum evaporation produced a dark red liquid that was purified by reverse phase using 5–95% H_2O / Acetonitrile gradient to afford the product as a white powder. The amino acid was mixed with 50% TFA/CH_2Cl_2 for 30 minutes with stirring. After concentration under vacuum, the remaining solution (1 to 2 mL volume) was added dropwise to 200 mL diethyl ether/hexane (1:1) and a white precipitate **1a** formed (2.0 g, 85% yield from **7**). The precipitate was filtered and dried under high vacuum.

(5*S*,8*S*)-1-Benzyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 1a: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 2.48 (1H, m), 2.85 (1H, dd, J=

6.8, 13.7), 3.58 (1H, d, J= 13.4), 3.74 (1H, d, J= 13.4), 4.55 (1H, dd, J= 6.8, 12.3), 4.71 (2H, s), 7.29–7.53 (10H, m); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 35.3, 42.8, 49.0, 59.7, 68.4, 127.2, 127.3, 127.6, 128.6, 128.9, 129.1, 132.2, 138.0, 154.9, 169.6, 174.2; IR (neat): 1775, 1718, 1495, 1414, 1181, 1134 cm^{-1}; $[\alpha]_D^{18}$ = +10.9 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 11.9 mins; HRMS-ESI: m/z Calculated for $C_{20}H_{20}N_3O_4$ $(M+H)^+$ 366.1448; Found: 366.1450.

Synthetic procedure for catalyst 1b—Starting from Cbz, t-Butyl Pro4(SS) amino acid **5** (728 mg, 2.0 mmol), catalyst **1b** was synthesized following the same synthetic procedure of **1a** with the exception of substituting 1-naphthylaldehyde for benzaldehyde in **step 1**.

(3*S*,5*S*)-1-[(Benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]-3-[(naphthanlen-1-ylmethyl)amino]pyrrolidine-3-carboxylic acid, 8: 807mg, 80% crude yield in Step 1; ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.38 (9H, s), 2.40 (1H, dd, J=8.1, 13.2), 3.00 (1H, dd, J=8.5, 13.1), 3.75 (1H, d= 11.3), 4.24 (1H, d, J= 11.3), 4.37 (1H, t, J= 7.9), 4.57 (2H, dd, J= 13.2, 22.5), 5.13(2H, s), 7.32–7.39 (5H, m), 7.53–7.64 (3H, m), 7.70 (1H, d), 7.98 (2H, t, J= 9.3), 8.24 (1H, d, J= 8.5); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 28.0, 28.1, 37.1, 46.5, 53.4, 59.4, 67.1, 81.8, 124.1, 125.7, 126.5, 127.0, 127.8, 128.3, 129.0, 129.1, 129.7, 130.8, 131.8, 133.9, 137.0, 154.1, 170.6, 171.7; HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 19.7 mins; HRMS-ESI: m/z Calculated for $C_{29}H_{33}N_2O_6$ $(M+H)^+$ 505.2333; Found: 505.2343.

7-Benzyl-8-*tert*-butyl(5*S*,8*S*)-1-(naphthalen-1-ylmethyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 13: ^{1}H NMR(500 MHz, d^6-DMSO, 350 K, δ): 1.20 (9H, s), 2.19 (1H, dd, J= 8.4, 13.7), 2.72 (1H, dd, J= 8.5, 13.7), 3.61 (1H, d, J= 11.8), 4.03 (1H, d, J= 11.8), 4.35 (1H, t, J=8.4), 5.06 (2H, s), 5.18 (2H, s), 7.28–7.33 (5H, m), 7.42–7.45 (1H, m), 7.47–7.63 (8H, m), 7.88 (1H, d), 7.98 (1H, d), 8.21 (1H, d); ^{13}C NMR (125 MHz, $CDCl_3$, 298 K, δ): 27.6, 35.4, 42.0, 49.6, 58.2, 66.1, 67.5, 81.9, 123.1, 125.3, 125.9, 126.1, 126.3, 127.0, 127.8, 128.0, 128.4, 129.0, 129.1, 129.3, 131.0, 131.3, 134.0, 136.0, 154.1, 154.7, 170.5, 173.2. IR (neat): 1694, 1403, 1349, 1149, 1124 cm^{-1}; $[\alpha]_D^{18}$ = −3.6 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r =27.6 mins; HRMS-ESI: m/z Calculated for $C_{36}H_{35}N_3NaO_6$ $(M+Na)^+$ 628.2418; Found: 628.2422.

(5*S*,8*S*)-1-(Naphthanlen-1-ylmethyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 1b: 592mg, 70% yield from **13**; ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 2.54 (1H, m), 2.98 (1H, dd, J= 6.7, 13.7), 3.66 (1H, d, J= 13.4), 3.83 (1H, d, J= 13.4), 4.57 (1H, dd, J= 6.7, 12.5), 5.23 (2H, s), 7.42–7.87 (9H, m), 7.88(1H, d, J= 7.8), 7.98 (1H, d, J= 7.5), 8.17 (1H, d, J= 8.5); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 34.6, 41.3, 48.4, 59.2, 68.0, 122.8, 123.5, 126.0, 126.5, 126.8, 127.3, 127.8, 128.6, 129.1, 129.2, 130.4, 132.2, 132.8, 133.6, 154.8, 169.0, 174.2; IR (neat): 1775, 1721, 1502, 1415, 1385, 1185, 1138 cm^{-1}; $[\alpha]_D^{18}$ = +13.1 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 14.3 mins; HRMS-ESI: m/z Calculated for $C_{24}H_{22}N_3O_4$ $(M+H)^+$ 416.1605; Found: 416.1611.

Synthetic procedure for catalyst 1c—Starting from Cbz, t-Butyl Pro4(SS) amino acid **5** (364 mg, 1.0 mmol), the synthesis of catalyst **1c** follows the same procedure as that of catalyst **1a** with the following changes: (1) 1-pyrenealdehyde substituted for benzaldehyde in step 1; (2) after the methanol was removed by concentration under vacuum, 10 ml of H_2O was added to the residue and 2 drops of 2N KOH (aq.) was added to assist the dissolution of the amino acid before adjusting the pH to 7 in step 1.

(3*S*,5*S*)-1-[(Benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]-3-[(pyren-1-ylmethyl)amino]pyrrolidine-3-carboxylic acid, 9: 462mg, 80% crude yield in Step 1; ^{1}H NMR (500HMz, d^6-DMSO, 350 K, δ): 1.41 (9H, s), 2.74 (1H, dd, J= 8.9, 13.1), 3.06 (1H, dd, J= 8.3, 12.8), 4.03 (1H, d, J= 11.4), 4.33 (1H, d, J= 11.4), 4.42 (1H, t, J= 8.2), 4.97 (2H, dd, J= 13.5, 23.9), 5.15 (2H, s), 7.31–7.40 (5H, m), 8.12 (1H, t, J= 7.7), 8.21 (2H, m), 8.31–8.39 (5H, m), 8.58 (1H, d, J= 9.3); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 28.0, 28.1, 36.2, 46.5, 52.8, 59.4, 67.1, 80.0, 123.6, 124.3, 124.6, 126.1, 126.0, 126.2, 126.5, 126.9, 127.7, 127.8, 128.3, 128.6, 128.8, 129.9, 130.8, 131.3, 132.1, 137.0, 154.1, 170.2, 170.8; HPLC analysis (C_{18} reverse phase, 30 mins, 5–95% H_2O/ACN with 0.1 % formic acid): T_r = 22.5 mins; HRMS-ESI: m/z Calculated for $C_{35}H_{35}N_2O_6$ $(M+H)^+$ 579.2490; Found: 579.2500.

7-Benzyl-8-*tert*-butyl(5*S*,8*S*)-2,4-dioxo-3-phenyl-1-(pyren-1-ylmethyl)-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 14: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.08 (9H, s), 2.13 (1H, dd, J= 8.5, 13.6), 2.69 (1H, dd, J= 8.5, 13.5), 3.66 (1H, d, J= 11.8), 4.05 (1H, d, J= 11.8), 4.33 (1H, t, J= 8.5), 5.03 (2H, s), 5.49 (2H, dd, J= 16.9, 29.6), 7.26–7.30 (5H, m), 7.43–7.46 (1H, m), 7.52–7.59 (4H, m), 8.10 (1H, m), 8.15–8.20 (3H, m), 8.28–8.34 (4H, m), 8.52 (1H, d, J= 9.3); ^{13}C NMR (125 MHz, $CDCl_3$, 298K., δ): 27.5, 35.4, 42.1, 49.4, 58.1, 66.1, 67.5, 81.8, 122.3, 124.6, 125.0, 125.1, 125.6, 125.7, 125.9, 126.3, 126.6, 127.3, 127.7, 127.9, 128.4, 128.7, 128.8, 129.1, 130.7, 131.3, 131.6, 136.0, 154.1, 154.9, 170.3, 173.2; IR (neat): 1839, 1620, 1486, 1387, 1332, 1116 cm^{-1}; $[\alpha]_D^{18}$ = −11.2 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 29.9 mins; HRMS-ESI: m/z Calculated for $C_{42}H_{37}N_3NaO_6$ $(M+Na)^+$ 702.2575; Found: 702.2569.

(5*S*,8*S*)-2,4-Dioxo-3-phenyl-1-(pyren-1-ylmethyl)-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 1c: 352mg, 73% yield from **14**. ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 2.56 (1H, t, J= 13.2), 3.09 (1H, dd, J= 6.6, 13.5), 3.64 (1H, d, J= 13.6), 3.87 (1H, d, J= 13.6), 4.57 (1H, dd, J= 6.7, 12.8), 5.53 (2H, s), 7.40–7.65 (5H, m), 8.10–8.48 (10H, m); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 34.1, 41.7, 48.2, 58.8, 67.8, 123.1, 123.7, 124.3, 124.4, 125.4, 125.8, 125.9, 126.9, 127.3, 127.4, 127.5, 127.9, 128.1, 128.7, 129.2, 130.4, 130.7, 130.9, 131.4, 132.2, 155.0, 168.8, 174.2; IR (neat): 1777, 1719, 1502, 1415, 1186, 1139 cm^{-1}; $[\alpha]_D^{18}$ = +3.5 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 17.4 mins; HRMS-ESI: m/z Calculated for $C_{30}H_{24}N_3O_4$ $(M+H)^+$ 490.1761; Found: 490.1768.

Synthetic procedure for catalyst 1d—Starting from Cbz, t-Butyl Pro4(SS) amino acid **5** (364 mg, 1.0 mmol), the synthesis of catalyst **1d** follows the same procedure as that of catalyst **1a** with the following exceptions: (1) 4-nitrobenzaldehyde substituted for benzaldehyde in step 1; (2) after the methanol was removed by concentration under vacuum, 10 ml of H_2O was added to the residue and 2 drops of 2N KOH (aq.) was added to assist the dissolution of the amino acid before adjusting the pH to 7 in step 1.

(3*S*,5*S*)-1-[(Benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]-3-([(4-nitrophenyl)methyl]amino)pyrrolidine-3-carboxylic acid, 10: 439mg, 88% crude yield in Step 1; ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.37 (9H, s), 2.22 (1H, dd, J= 6.8, 13.1), 2.82 (1H, dd, J= 8.8, 13.0), 3.56 (1H, d= 11.2), 4.00–4.08 (3H, m), 4.32 (1H, t, J=7.6), 5.10 (2H, s), 7.30–7.38 (5H, m), 7.68 (2H, d, J= 8.7), 8.19 (2H, d, J= 8.7); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 28.0, 28.1, 38.1, 48.3, 54.1, 59.3, 66.9, 81.6, 123.6, 127.8, 128.2, 128.7, 130.2, 137.1, 145.7, 147.7, 154.1, 170.6, 172.9; HPLC analysis (C_{18} reverse phase, 30 mins, 5–95% H_2O/ACN with 0.1 % formic acid): T_r = 18.7 mins; HRMS-ESI: m/z Calculated for $C_{25}H_{30}N_3O_8$ $(M+H)^+$ 500.2027; Found: 500.2032.

7-Benzyl-8-*tert*-butyl(5*S*,8*S*)-1-[(4-nitrophenyl)methyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 15: ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.34 (9H, s), 2.21 (1H, dd, J= 8.0, 13.8), 2.83 (1H, dd, J= 8.7, 13.8), 3.61 (1H, d, J= 11.9), 4.07 (1H, d, J= 11.9), 4.42 (1H, t, J= 8.3), 4.82 (2H, dd, J= 17.3, 25.4), 5.09 (2H, s), 7.30–7.34 (5H, m), 7.42 (1H, m), 7.48–7.56 (4H, m), 7.68 (2H, d, J= 8.8), 8.19 (2H, d, J= 8.8); ^{13}C NMR (125 MHz, $CDCl_3$, 298K, δ): 27.8, 37.3, 42.8, 51.6, 58.4, 66.8, 67.8, 82.6, 124.1, 125.7, 128.0, 128.3, 128.5, 129.2, 131.1, 135.8, 144.3, 147.6, 154.1, 154.9, 171.0, 172.7; IR (neat): 1704, 1596, 1516, 1493, 1402, 1340, 1125 cm^{-1}; $[\alpha]_D^{18}$ = +0.75 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 25.8 mins; HRMS-ESI: m/z Calculated for $C_{32}H_{32}N_4NaO_8$ $(M+Na)^+$ 623.2112; Found: 623.2111.

(5*S*,8*S*)-1-[(4-Nitrophenyl)methyl]-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 1d: 290mg, 63% yield from **15**; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 2.43 (1H, t, J= 13.2), 2.95 (1H, dd, J=6.6, 13.5), 3.51 (1H, d, J= 13.6), 3.74 (1H, d, J= 13.5), 4.53 (1H, dd, J= 6.6, 12.8), 4.87 (2H, s), 7.41–7.54 (5H, m), 7.72 (2H, d, J= 8.8), 8.24 (2H, d, J= 8.8); ^{13}C NMR (125 MHz, DMSO, 350 K, δ): 34.1, 42.6, 48.3, 58.7, 67.5, 124.0, 127.2, 128.3, 128.7, 129.2, 132.0, 145.9, 147.2, 154.9, 168.7, 173.9; IR (neat): 1777, 1718, 1517, 1413, 1345 cm^{-1}; $[\alpha]_D^{18}$ = +1.1 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 12.7 mins; HR-MS $(M+H)^+$ Calculated for $C_{20}H_{19}N_4O_6^+$: 411.1299; found: 411.1303.

Synthetic procedure for catalyst 1e—Starting from Cbz, t-Butyl Pro4(SS) amino acid **5** (364 mg, 1.0 mmol), the synthesis of catalyst **1e** follows the same procedure as that of catalyst **1a** with the following changes: (1) 4-methoxybenzaldehyde substituted for benzaldehyde in step 1; (2) after the methanol was removed by concentration under vacuum, 10 ml of H_2O was added to the residue and 2 drops of 2N KOH (aq.) was added to assist the dissolution of the amino acid before adjusting the pH to 7 in step 1.

(3*S*,5*S*)-1-[(Benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]-3-([(4-methoxyphenyl)methyl]amino)pyrrolidine-3-carboxylic acid, 11: 411mg, 85% crude yield in Step 1; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.40 (9H, s), 2.38 (1H, dd, J=8.6, 13.3), 2.92 (1H, dd, J= 8.4, 13.2), 3.72 (1H, d, J= 11.4), 3.79 (3H, s), 4.10 (1H, d, J= 12.6), 4.17 (2H,m), 4.35 (1H, t, J= 8.3), 5.12 (2H, s), 6.99 (2H, d, J= 8.7), 7.32–7.42 (7H, m); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 28.0, 28.1, 39.1, 48.5, 55.0, 55.7, 59.5, 66.6, 81.1, 114.2, 127.7, 128.1, 128.7, 129.8, 132.3, 137.3, 154.2, 159.0, 171.0, 174.4; HPLC analysis (C_{18} reverse phase, 30 mins, 5–95% H_2O/ACN with 0.1 % formic acid): T_r = 17.4 mins; HRMS-ESI: m/z Calculated for $C_{26}H_{33}N_2O_7$ $(M+H)^+$ 485.2282; Found: 485.2292.

7-Benzyl-8-*tert*-butyl(5*S*,8*S*)-1-[(4-methoxyphenyl)methyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 16: ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.36 (9H, s), 2.20 (1H, dd, J= 8.3, 13.8), 2.69 (1H, dd, J= 8.6, 13.7), 3.61 (1H, d, J= 11.8), 3.76 (3H, s), 3.97 (1H, d, J= 11.8), 4.38 (1H, t, J= 8.4), 4.62 (2H, s), 5.09 (2H, s), 6.91 (2H, d, J= 8.7), 7.28–7.38 (7H, m), 7.42 (1H, m), 7.47–7.53 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 298K, δ): 27.8, 36.2, 42.9, 50.2, 55.3, 58.3, 66.2, 67.6, 82.1, 114.4, 125.8, 127.8, 128.1, 128.3, 128.5, 128.9, 129.1, 129.2, 129.4, 131.3, 136.1, 154.1, 154.7, 159.4, 170.8, 173.3; IR (neat): 1682, 1607, 1493, 1399, 1344, 1239, 1121 cm^{-1}; $[\alpha]_D^{18}$ = −4.0 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 25.9 mins; HRMS-ESI: m/z Calculated for $C_{33}H_{35}N_3NaO_7$ $(M+Na)^+$ 608.2367; Found: 608.2377.

(5*S*,8*S*)-1-[(4-Methoxyphenyl)methyl]-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 1e: 207mg, 48% yield from **16**; ^{1}H NMR(500 MHz, d^{6}-DMSO, 350 K, δ): 2.46 (1H, m), 2.80 (1H, dd, J= 6.7, 13.6), 3.57 (1H, d, J=13.3), 3.70 (1H, d, J=13.4), 3.76 (3H, s), 4.54 (1H, dd, J=6.8, 12.1), 4.62 (2H, s), 6.91 (2H, d, J=8.7), 7.34 (2H, d, J=8.7), 7.39–7.43 (1H, m), 7.49–7.51 (4H, d, J=4.3); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 34.5, 42.6, 48.3, 55.6, 58.9, 67.9, 114.6, 127.1, 128.5, 129.0, 129.1, 129.8, 132.3, 154.8, 159.3, 168.6, 173.9; IR (neat): 1775, 1719, 1513, 1414, 1247, 1179, 1135 cm^{-1}; $[\alpha]_D^{18}$ = +7.8 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 12.2 mins; HRMS-ESI: m/z Calculated for $C_{21}H_{22}N_3O_5$ $(M+H)^+$ 396.1554; Found: 396.1562.

Synthetic procedure for catalyst 2a—The synthesis of catalyst **2a** follows the same procedure as that of catalyst **1a** with the change of beginning with Cbz, t-Butyl Pro4(SR) amino acid **6** (364 mg, 1.0 mmol) rather than Cbz, t-Butyl Pro4(SS) amino acid **5**.

(3*R*,5*S*)-3-(Benzylamino)-1-[(benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]pyrrolidine-3-carboxylic acid, 18: 341mg, 75% crude yield in Step 1; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.38 (9H, s), 2.58 (1H, dd, J=5.6, 14.1), 2.88 (1H, t, J=9.0), 3.84 (1H, d, J=12.5), 4.07–4.16 (3H, m), 4.51 (1H, t, J=6.7), 5.11 (2H, s), 7.30–7.48 (10H, m); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 28.1, 28.2, 39.0, 48.4, 54.7, 59.5, 66.7, 81.2, 127.1, 127.8, 128.1, 128.3, 128.5, 128.7, 137.3, 140.8, 154.5, 171.2, 173.5; HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 16.5 mins; HRMS-ESI: m/z Calculated for $C_{25}H_{31}N_2O_6$ $(M+H)^+$ 455.2177; Found: 455.2181.

7-Benzyl-8-*tert*-butyl(5*R*,8*S*)-1-benzyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 20: ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.37 (9H, s), 2.40 (1H, dd, J=6.9, 14.6), 2.77 (1H, dd, J=9.4, 14.3), 3.63 (1H, d, J=12.1), 3.86 (1H, d, J=11.0), 4.35 (1H, broad), 4.60 (2H, broad), 5.05 (1H, d, J=12,1), 7.28–7.35 (11H, m), 7.50 (4H, d, J=4.4); ^{1}H NMR(500 MHz, $CDCl_3$, 298K, δ, rotamersobserved): 1.37–1.45 (9H, d), 2.41–2.62 (2H, m), 3.76 (0.5H, d, J=11.8), 3.87 (0.5H, dd, J=11.8), 3.91 (0.5H, d, J=12.1), 3.99 (0.5H, d, J=12.1), 4.14 (0.5H, dd, J=6.8, 9.3), 4.43–4.51 (1.5H, m), 4.76 (0.5H, d, J=15.8), 4.84 (0.5H, d, J=15.8), 4.92 (0.5H, d, J=12.2), 5.11 (0.5H, d, J=12.2), 5.17 (1H, tt, J=12.5), 7.23–7.53 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 298K, δ): 27.8, 27.9, 38.6, (29.9, 44.5, 54.6, 58.9, 59.5, 67.5, 68.4, 69.3, 82.5, 125.8, 127.5, 127.6, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.9, 129.1, 131.5, 135.9, 136.0, 136.6, 136.7, 153.4, 153.7, 154.7, 154.8, 169.6, 169.8, 171.0, 171.3; IR (neat): 1702, 1492, 1406, 1353, 1139 cm^{-1}; $[\alpha]_D^{18}$ = −88.1 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 25.9 mins; HRMS-ESI: m/z Calculated for $C_{32}H_{33}N_3NaO_6$ $(M+Na)^+$ 578.2262; Found: 578.2267.

(5*R*,8*S*)-1-Benzyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 2a: 227mg, 63% yield from **20**; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 2.61 (1H, dd, J= 9.7, 14.5), 2.71 (1H, dd, J= 5.9, 14.5), 3.54 (1H, d, J= 13.2), 3.80 (1H, d, J= 13.2), 4.62 (1H, t, J= 6.0), 4.71 (2H, dd, J= 16.9, 51.8), 7.25–7.55 (10H, m); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 35.1, 43.1, 49.7, 58.8, 68.0, 127.2, 127.3, 127.7, 128.6, 129.0, 129.1, 132.2, 137.9, 155.0, 169.3, 173.3; IR (neat): 1776, 1714, 1494, 1415, 1185, 1135 cm^{-1}; $[\alpha]_D^{18}$ = +13.1 (MeOH); HPLC analysis (C_{18} reverse phase, 30 mins, 5–95 % H_2O/ACN with 0.1 % formic acid): T_r = 11.6 mins; HRMS-ESI: m/z Calculated for $C_{20}H_{20}N_3O_4$ $(M+H)^+$ 366.1448; Found: 366.1454.

Synthetic procedure for catalyst 2b—The synthesis of catalyst **2b** follows the same procedure as that of catalyst **1b** with the exception of Cbz, t-Butyl Pro4(SR) amino acid **6** (364 mg, 1.0 mmol), substituted for Cbz, t-Butyl Pro4(SS) amino acid **5**.

(3*R*,5*S*)-1-[(Benzyloxy)carbonyl]-5-[(*tert*-butoxy)carbonyl]-3-[(naphthanlen-1-ylmethyl)amino]pyrrolidine-3-carboxylic acid, 19: 439mg, 87% crude yield in Step 1; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.41 (9H, s), 2.63 (1H, d, J=13.5), 2.94 (1H, t, J=9.9), 3.89 (1H, d, J=12.4), 4.14 (1H, d, J=12.5), 4.50–4.61 (3H, m), 5.12 (2H, s), 7.30–8.30 (12H, m); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 28.0, 28.1, 45.6, 53.8, 59.1, 67.1, 81.9, 124.0, 124.1, 125.7, 126.6, 127.2, 128.0, 128.3, 128.7, 129.1, 129.2, 129.4, 129.6, 130.0, 130.1, 131.8. 134.0. 136.9, 153.9, 170.2; HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 19.2 mins; HRMS-ESI: m/z Calculated for $C_{29}H_{33}N_2O_6$ $(M+H)^+$ 505.2333; Found: 505.2342.

7-Benzyl-8-*tert*-butyl(5*R*,8*S*)-1-(naphthalen-1-ylmethyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-7,8-dicarboxylate, 21: ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 1.33 (9H, s), 2.41 (1H, dd, J=6.1, 14.6), 2.78 (1H, s), 3.63 (1H, d, J=12.1), 3.87 (1H, broad), 4.18 (1H, broad), 4.72 (1H, broad), 4.88 (1H, broad), 5.13 (1H, s), 7.19 (2H, d, J=6.8), 7.31 (3H, m), 7.39–7.57 (9H, m), 7.86 (1H, d, J=8.2), 7.96 (1H, d, J=7.2), 8.19 (1H, d, J=7.9); ^{1}H NMR(500 MHz, $CDCl_3$, 298 K, δ, rotamers observed): 1.31–1.41 (9H, d), 2.14 (0.5H, dd, J=9.7, 14.6), 2.33 (0.5H, dd, J=10.5, 14.7), 2.38–2.49 (1H, m), 3.67 (0.5H, d, J=11.8), 3.81–3.85 (1H, m), 3.91 (0.5H, d, J=12.2), 4.09 (0.5H, d, J=12.2), 4.24 (0.5H, dd, J=5.8, 9.6), 4.87 (1H, dd, J=15.9, 29.5), 5.03 (1H, dd, J=12.3, 15.2), 5.09–5.59 (2H, m), 7.22–7.60 (14H, m), 7.78–7.92 (2H, m), 8.16–8.20 (1H, t, J=6.7); ^{13}C NMR (125 MHz, $CDCl_3$, 298 K, δ): 27.7, 27.8, 38.0, 39.5, 42.7, 43.0, 54.0, 58.9, 59.5, 67.4, 68.6, 69.6, 82.4, 123.0, 123.2, 125.1, 125.2, 125.8, 125.9, 126.2, 126.2, 126.9, 127.1, 127.2, 127.5, 128.0, 128.1, 128.3, 128.4, 128.5, 128.5, 129.1, 129.4, 131.0, 131.1, 131.2, 131.2, 131.5, 131.5, 133.9, 133.9, 136.0, 136.0, 153.5, 154.5, 154.7, 169.5, 169.7, 171.7, 171.8; IR (neat): 1720, 1704, 1647, 1417, 1270 cm^{-1}; $[\alpha]_D^{18}$ = −31.4 (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 27.5 mins; HRMS-ESI: m/z Calculated for $C_{36}H_{35}N_3NaO_6$ $(M+Na)^+$ 628.2418; Found: 628.2423.

(5*R*,8*S*)-1-(Naphthanlen-1-ylmethyl)-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid.TFA, 2b: 244mg, 53% yield from **21**; ^{1}H NMR (500 MHz, d^{6}-DMSO, 350 K, δ): 2.71 (1H, dd, J= 10.0, 14.6), 2.87 (1H, dd, J= 4.8, 14.6), 3.62 (1H, d, J= 13.2), 3.88 (1H, d, J= 13.2), 4.63 (1H, dd, J= 4.9, 10.1), 5.20 (2H, s), 7.35–7.70 (9H, m), 7.89 (1H, d, J= 8.2), 8.00 (1H, d, J= 7.5), 8.13 (1H, d, J= 8.3); ^{13}C NMR (125 MHz, d^{6}-DMSO, 350 K, δ): 34.8, 41.7, 49.6, 58.7, 68.0, 123.2, 123.6, 126.0, 126.5, 126.7, 127.3, 127.9, 128.6, 129.0, 129.1, 130.5, 132.2, 132.7, 133.6, 154.9, 169.4, 173.7; IR (neat): 1777, 1719, 1502, 1418, 1187, 1137 cm-1; $[\alpha]_D^{18}$ = +2.6 (MeOH); HPLC analysis (C_{18} reverse phase, 30 mins, 5–95 % H_2O/ACN with 0.1 % formic acid): Tr = 14.2mins; HRMS-ESI: m/z Calculated for $C_{24}H_{22}N_3O_4$ $(M+H)^+$ 416.1605; found: 416.1608.

Synthetic procedure for catalyst 1f—To a solution of Cbz, t-Butyl Pro4(SS) amino acid **5** (547 mg, 1.5 mmol, 1.0 eq) in methanol, acetaldehyde (102 μL, 1.8 mmol, 1.2 eq) was added in one portion at room temperature and stirred for 30 minutes, followed by addition of sodium cyanoborohydride (142 mg, 2.3 mmol, 1.5 eq). After the reaction was complete after 20 hours, as monitored by LC-MS, phenyl isocyanate (327 μL, 3.0 mmol, 3.0 eq) was added and the reaction was stirred at room temperature for 40 hours until completion, as indicated by LC-MS. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (5 mL). To this solution, 33% HBr/AcOH (7 mL) was added and the reaction was stirred for 2 hours at room temperature until the Cbz- and t-

Butyl- groups were removed completely, as indicated by LC-MS. After the removal of solvent under vacuum, the residue was purified by reverse phase. The purified compound was added to 50% TFA/CH_2Cl_2 (20 mL) and stirred at room temperature for 30 minutes. After concentration under vacuum, the remaining solution (1 to 2 mL volume) was added dropwise to 100 mL diethyl ether/hexane (1:1) and a white precipitate **1f** formed (97 mg, 15% overall yield from **5**). The precipitate was filtered and dried under high vacuum.

(5*S*,8*S*)-1-Ethyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid. TFA, 1f: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.27 (3H, t, J= 7.0), 2.55 (1H, m), 2.86 (1H, dd, J= 6.8, 13.7), 3.48 (2H, dd, J= 7.2, 14.4), 3.61 (1H, d, J=13.4), 3.72 (1H, d, J=13.4), 4.57 (1H, dd, J=6.9, 12.2), 7.39–7.52 (5H, m); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 14.7, 35.1, 35.6, 49.9, 59.5, 68.3, 127.0, 128.4, 129.0, 132.4, 154.1, 169.7, 174.2; IR (neat): 1774, 1718, 1502, 1421, 1186, 1138 cm-1; $[\alpha]_D^{18}$ = +11.1 (MeOH); HPLC analysis (C_{18} reverse phase, 30 mins, 5–95 % H_2O/ACN with 0.1 % formic acid): Tr= 7.7 mins; HRMS-ESI: m/z Calculated for $C_{15}H_{18}N_3O_4$ $(M+H)^+$ 304.1292; Found: 304.1293.

Synthetic procedure for catalyst 2c—The synthesis of catalyst **2c** follows the same procedure as that of catalyst **1f** with the exception of Cbz, t-Butyl Pro4(SR) amino acid **6** (364 mg, 1.0 mmol) substituted for Cbz, t-Butyl Pro4(SS) amino acid **5**.

(5*R*,8*S*)-1-Ethyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4,4]nonane-8-carboxylic acid. TFA, 2c: 60mg, 14% overall yield from **6**; 1H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.28 (3H, t, J= 7.0), 2.70–2.82 (2H, m), 3.49 (2H, m), 3.63 (1H, d, J= 13.2), 3.82 (1H, d, J= 13.2), 4.76 (1H, dd, J=6.4, 9.5), 7.39–7.51 (5H, m); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 15.0, 35.6, 37.3, 52.6, 59.7, 69.2, 126.9, 128.3, 129.0, 132.6, 154.2, 171.4, 173.9; IR (neat): 1775, 1719, 1502, 1423, 1187, 1137 cm-1; $[\alpha]_D^{18}$ = +9.6 (MeOH); HPLC analysis (C_{18} reverse phase, 30 mins, 5–95 % H_2O/ACN with 0.1 % formic acid): Tr= 7.4 mins; HRMS-ESI: m/z Calculated for $C_{15}H_{18}N_3O_4$ $(M+H)^+$ 304.1292; found: 304.1285.

Synthetic procedure for 17—In a flame dried 50 mL round-bottom flask under argon, 1-((Benzyloxy)carbonyl)-5-(*tert*-butoxycarbonyl)-3-(benzylamino)pyrrolidine-3-carboxylic acid **7** (454 mg, 1.0 mmol, 1 eq) and HOAt (1.36g, 10.0 mmol, 10.0 eq) were dissolved in 18 mL CH_2Cl_2/DMF (2:1) for 10 minutes followed by addition of DIC (188 μL, 1.2 mmol, 1.2 eq). The reaction was stirred at room temperature for 2 hours. To the reaction, a suspension of 1-Naphthyl-Aib-OH (292 mg, 1.2 mmol, 1.2 eq), DIPEA (416 μL, 2.4 mmol, 2.4 eq) in 6 mL DMF was added in one portion. The reaction was stirred at room temperature for 12 hours. To the reaction mixture, DIC (188 μL, 1.2 mmol, 1.2 eq) was added in one portion and the reaction was stirred at room temperature for an additional 12 hours until completion, as determined by LC-MS. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (20 mL) and the product was then extracted with EtOAc (100 mL followed by 2x50 mL). The combined organic EtOAc layers were washed sequentially with saturated $NaHCO_3$ (aq.), brine, and dried over anhydrous Na_2SO_4. The $Na_2SO_4$was removed by filtration and the filtrate was concentrated under vacuum to produce a yellow solid crude product. The pure white powder product **17** (440 mg, 67% yield) was obtained after purification by C_{18} reverse phase chromatography (5–100% Water/ Acetonitrile).

2-Benzyl-3-*tert*-butyl(3*S*,5*S*)-6-benzyl-8,8-dimethyl-9-(naphthalen-1-ylmethyl)-7,10-dioxo-2,6,9-triazaspiro[4,5]decane-2,3-dicarboxylate, 17: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.35 (9H, s), 1.55 (3H, s), 1.59 (3H, s), 2.35 (1H, dd, J=7.6, 14.1), 2.84 (1H, dd, J=9.2, 14.0), 3.77 (1H, d, J=12.0), 4.08 (1H, d, J=12.0), 4.36 (1H, t, J=7.7), 4.67 (1H, d, J=16.4), 4.85 (1H, d, J=16.4), 5.07 (2H, s), 5.19 (2H., d, J=11.9), 7.20–7.65 (14H,

m), 7.81 (1H, d, J=8.3), 7.96 (1H, d, J=8.4). 8.17 (1H, d, J=8.4); ^{13}C NMR (125 MHz, $CDCl_3$, 298K, δ): 26.6, 27.3, 27.7, 39.8, 43.7, 46.9, 55.0, 60.1, 61.8, 66.9, 67.4, 81.9, 122.2, 122.7, 125.4, 125.9, 126.2, 126.5, 127.4, 127.7, 127.8, 127.9, 128.4, 128.9, 129.1, 130.5, 131.8, 133.8, 136.1, 137.4, 154.0, 168.8, 170.6, 171.7; IR (neat): 1698, 1644, 1395, 1345, 1121 cm^{-1}; $[\alpha]_D^{18} = -2.3$ (MeOH); HPLC analysis (C_{18} reverse phase, 40 mins, 5–100% H_2O/ACN with 0.1 % formic acid): T_r = 28.7 mins; HRMS-ESI: m/z Calculated for $C_{40}H_{44}N_3O_6$ $(M+H)^+$ 662.3225; Found: 662.3234.

Synthetic procedure for catalyst 3—33% HBr/AcOH (7 mL) was added to the solution of compound **17** (440 mg, 0.67 mmol) in CH_2Cl_2 (5 mL) in one portion and the reaction was stirred at room temperature for 2 hours. Removal of solvent under vacuum resulted in dark red liquid that was reverse phase purified with 5–95% Water/Acetonitrile gradient. After lyophilization, the white powder was dissolved in 50% TFA/CH_2Cl_2 (50 mL) and stirred for 30 minutes at room temperature. After concentration under vacuum, the remaining solution (1 to 2 mL volume) was added dropwise to 100 mL diethyl ether/hexane (1:1) and a white precipitate **3** formed (250 mg, 64% yield). The precipitate was filtered and dried under high vacuum.

(3*S*,5*S*)-6-Benzyl-8,8-dimethyl-9-(naphthalen-1-ylmethyl)-7,10-dioxo-2,6,9-triazaspiro[4,5]decane-3-carboxylic acid.TFA, 3: ^{1}H NMR (500 MHz, d^6-DMSO, 350 K, δ): 1.57 (3H, s), 1.59 (3H, s), 2.58 (1H, t, J=13.6), 2.85 (1H, dd, J=7.4, 13.9), 3.64 (1H, d, J=13.1), 3.80 (1H, d, J=13.1), 4.59 (1H, dd, J=7.5, 11.4), 4.74 (1H, d, J=16.6), 4.90 (1H, d, J=16.6), 5.22 (2H, d, J=3.4), 7.23–7.63 (9H, m), 7.82 (1H, d, J=8.2), 7.95 (1H, d, J=7.1), 8.17 (1H, d, J=8.4); ^{13}C NMR (125 MHz, d^6-DMSO, 350 K, δ): 26.4, 26.9, 39.2, 44.3, 46.5, 52.2, 60.3, 61.8, 68.6, 122.8, 123.4, 126.0, 126.1, 126.3, 126.6, 127.2, 127.4, 129.1, 130.5, 133.0, 133.7, 138.2, 168.6, 169.5, 169.8; IR (neat): 1654, 1403, 1363, 1303, 1199 cm^{-1}; $[\alpha]_D^{18} = +8.8$ (MeOH); HPLC analysis (C_{18} reverse phase, 30mins, 5–95 % H_2O/ACN with 0.1 % formic acid): T_r =16.1 mins; HRMS-ESI: m/z Calculated for $C_{28}H_{30}N_3O_4$ $(M+H)^+$ 472.2231; Found: 472.2236.

Typical procedure for aldol reaction catalyzed by 1a–1f, 2a–2b and 3—To a vial containing **1a** (6.3 mg, 0.0132 mmol, 0.01 eq) and 3 mL H_2O, a mixture of cyclohexanone (1.37 mL, 13.2 mmol, 10.0 eq) and 4-nitrobenzaldehyde (200 mg, 1.32 mmol, 1.0 eq) was added. The reaction was stirred at room temperature until completion as determined by TLC. The reaction was quenched by addition of 6 mL saturated NH_4Cl (aq.) and extracted with $CHCl_3$ (10 mL + 2x5 mL). The combined organic layers were concentrated to afford the crude product. The diastereoselectivity was determined by proton NMR of the crude product. Purification by silica gel chromatography using 10–30% EtOAc/Hexanes afforded the pure aldol reaction product (316 mg, 96% yields). The enantioselectivity was determined by chiral HPLC with a Chiralpak AD column (UV detection set at 254 nm, flow rate of 0.5 mL/min, 20% i-PrOH/hexane as the eluting solvent).

Procedure for catalyst recycling—To a vial containing **1a** (6.3 mg, 0.0132 mmol, 0.01 eq) and 3 mL H_2O, mixture of cyclohexanone (1.37 mL, 13.2 mmol, 10.0 eq) and 4-nitrobenzaldehyde (200 mg, 1.32 mmol, 1.0 eq) was added. The reaction was stirred at room temperature until completion, as determined by TLC. Hexanes (6 mL) was added to the reaction mixture and mixed for 5 minutes. The hexanes layer was removed carefully by pipette. To the aqueous layer, a fresh aliquot of cyclohexanone (1.37 mL, 13.2 mmol, 10.0 eq) and 4-nitrobenzaldehyde (200 mg, 1.32 mmol, 1.0 eq) was added for the second recycling round. The recycling procedure was then repeated for a third time. The combined organic layers were evaporated under vacuum and the residue was analyzed by proton NMR with $CDCl_3$ as solvent to determine the diastereoselectivity. The yield was determined after

purification of the crude products by silica gel using 20% EtOAc/hexanes. The enantioselectvity was determined by injection of the purified products into an HPLC with a Chiralpak AD column (UV detection set at 254 nm, flow rate of 0.5 mL/min, 20% i-PrOH/ hexane as the eluting solvent).

Typical kinetics experiment for 1a, 2a and 1f catalyzed aldol reaction—To a vial containing **1a** (6.3 mg, 0.0132 mmol, 0.01 eq) and 3 mL H_2O, a mixture of cyclohexanone (1.37 mL, 13.2 mmol, 10.0 eq) and 4-nitrobenzaldehyde (200 mg, 1.32 mmol, 1.0 eq) was added. The reaction was stirred vigorously at room temperature. At specific time points (shown in supporting information), 200 μL of the reaction mixture was taken out by pipette and added to a vial containing 1 mL of saturated NH_4Cl (aq.), followed by 600 μL $CDCl_3$. After shaking the vial and two layers formed, the $CDCl_3$ layer was taken out by pipette carefully for analysis by 1D H-NMR. The starting material / product ratio was determined by the integration of the aldehyde proton peak (10.11 ppm) versus the proton peak of α position of the hydroxyl group (5.42 ppm for syn products, 4.86 ppm for anti products).

Quantum mechanical calculations—All of the computations were performed in *Gaussian 09*. [16] The geometries were fully optimized by M06-2X/6-31G(d) either in the gas phase or using the SMD model to account for the solvation effects of water. The computations in water as solvent were performed using the SMD model parameters[14] along with the IEF-PCM algorithm[17] for bulk electrostatics as implemented in *Gaussian 09*. [14, 16] The reported free energies were computed from partition functions evaluated using a quasiharmonic approximation in both the gas phase and the solution.[14c] This approximation is the same as the usual harmonic approximation, except that the vibrational frequencies lower than 100 cm^{-1} are raised to 100 cm^{-1}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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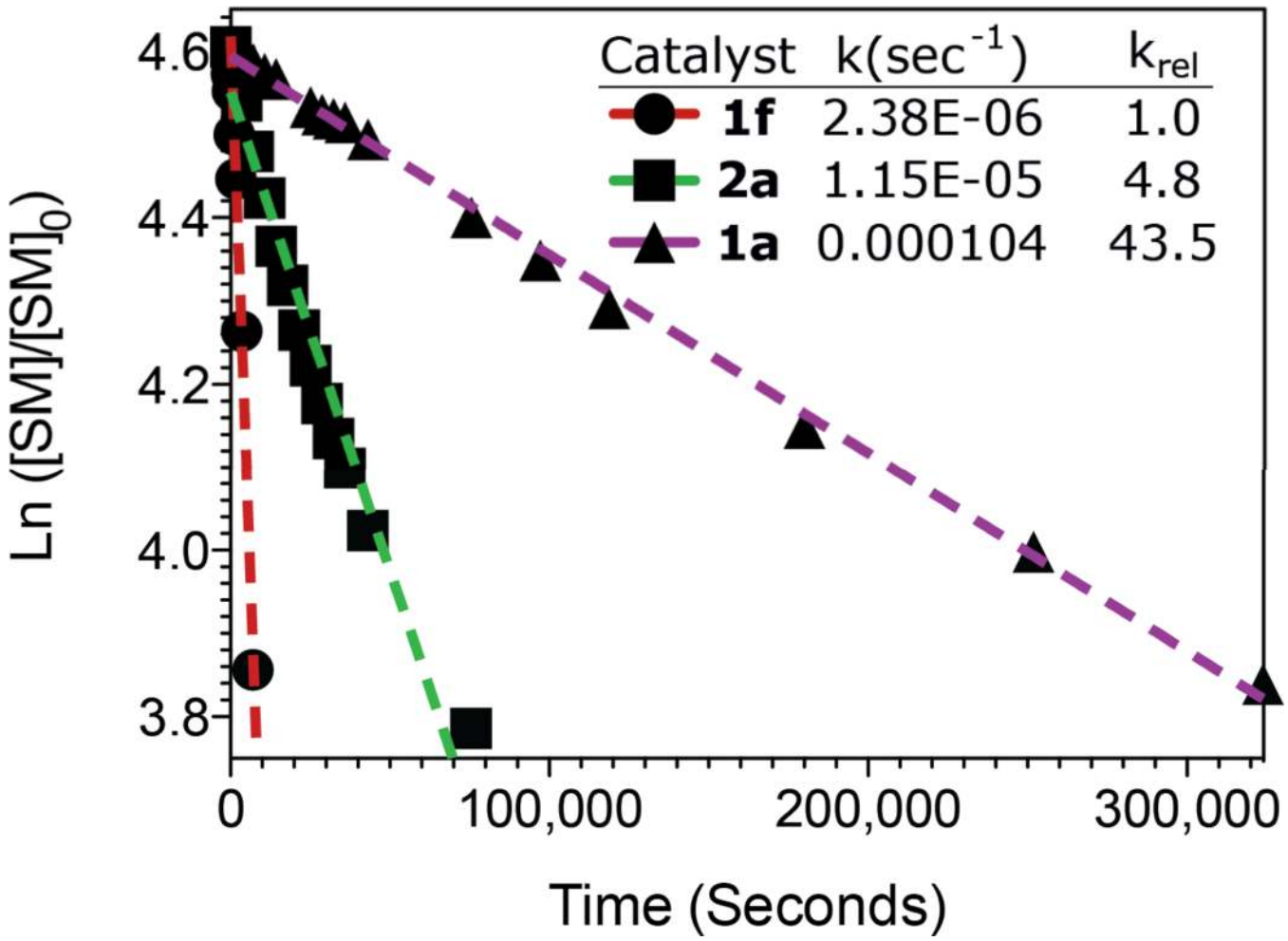


Figure 1.
Linearized kinetic data for the aldol reactions of cyclohexanone and *para*-nitrobenzaldehyde catalyzed by **1a, 2a** and **1f** in water

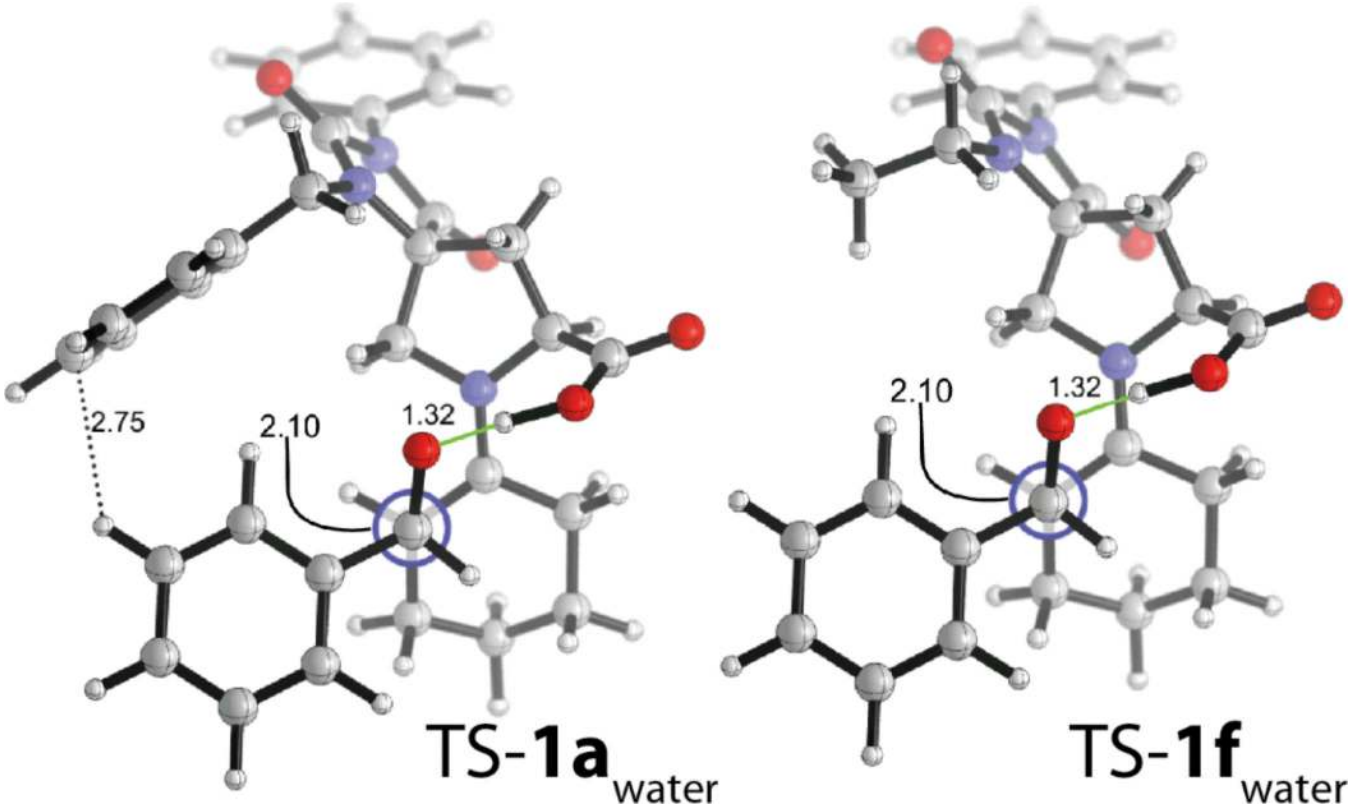
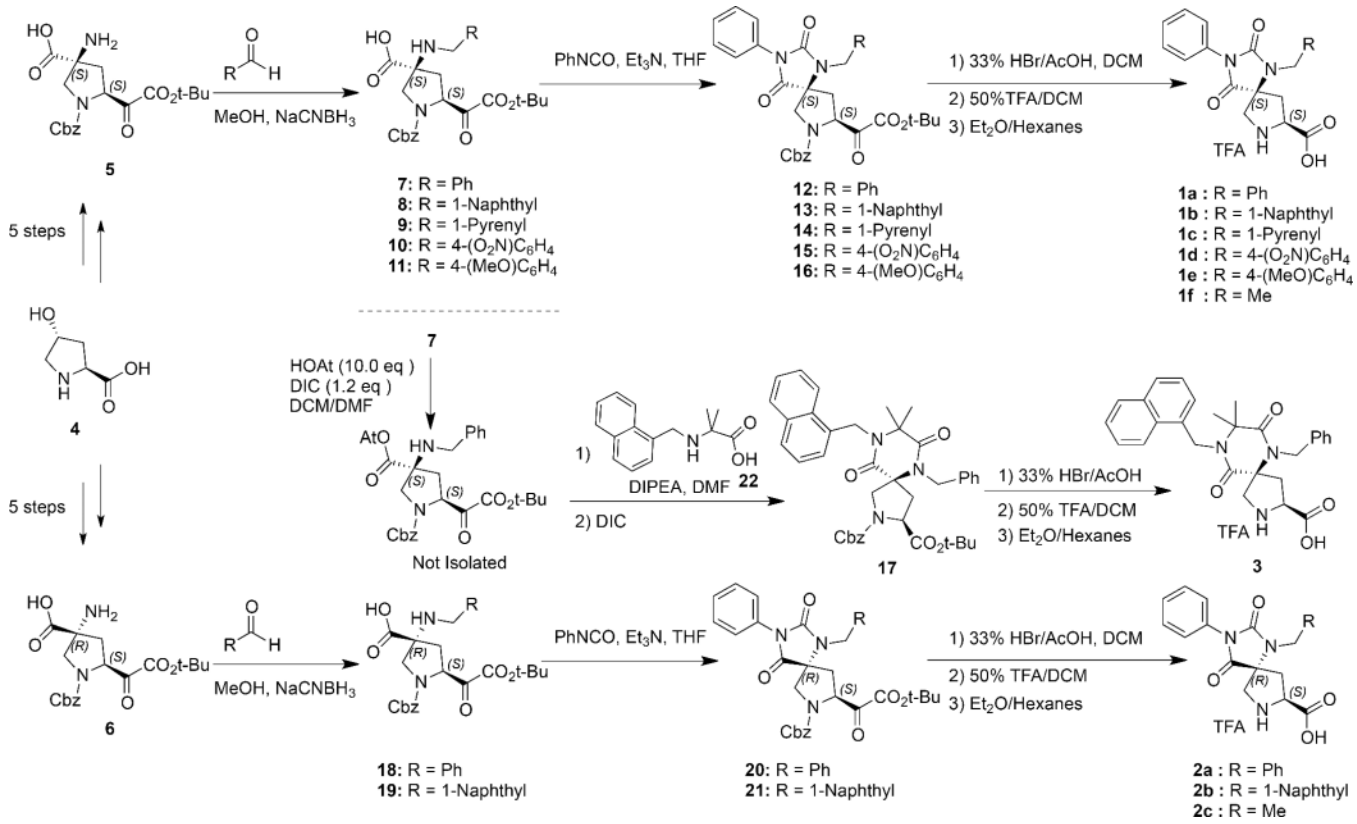


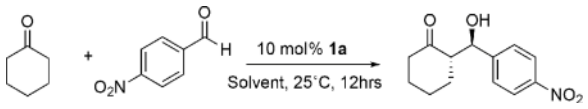
Figure 2.
Optimized transition structures for the aldol addition step catalyzed by **1a** and **1f** in water



Scheme 1.
Catalyst synthesis.
[a]See reference 10.

Table 1

Solvent screening.



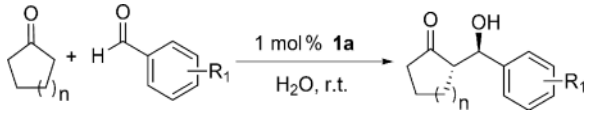
		Product: SM		
Entry	**Solvent**	**Ratio[a]**	**dr[b]**	**ee[c] (%)**
1	H_2O	>98:2	>98:2	>98
2	MeOH	76:24	>98:2	>98
3	IPA	>98:2	91:9	94
4	t-BuOH	>98:2	90:10	94
5	DMSO	60:40	78:22	89
6	DMF	41:59	79:21	87
7	DCM	97:3	86:14	96
8	MeCN	79:21	88:12	92
9	Toluene	98:2	96:4	96
10	Et_2O	>98:2	95:5	93
11	EtOAc	>98:2	94:6	93
12	Hexane	>98:2	95:5	97
13	THF	>98:2	94:6	95
14	Cyclohexanone	>98:2	92:8	93

[a,b]The diastereomeric ratios were determined by 1D ^{1}H-NMR.

[c]The ee values were determined by HPLC using a Chiralpak AD column.

Table 2

Substrate screening



Entry	n	R_1	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	2	*p*-NO_2	12	96	>98:2	>98
2	1	*p*-NO_2	9	98	95:5	>98
3[d]	3	*p*-NO_2	48	77	80:20	94
4	2	*o*-NO_2	19	92	>98:2	>98
5	2	*m*-NO_2	13	98	>98:2	>98
6	2	*p*-CN	12	94	>98:2	>98
7	2	*p*-Br	100	80	97:3	>98
8	2	*p*-Cl	100	64	97:3	>98
9	2	*p*-OMe	120	18	92:8	>98
10	2	CO_2Me	13	97	98:2	>98
11[e]	2	*p*-NO_2	78	96	>98:2	>98
12	2	H	100	74	95:5	98

[a] Isolated yield.

[b] The diastereomeric ratios were determined by ^{1}H-NMR of the crude mixture.

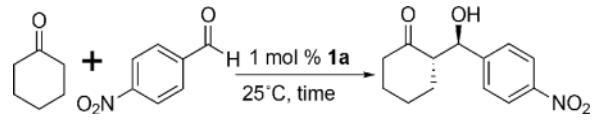
[c] The ee values were determined by HPLC using a Chiralpak AD column.

[d] 10 mol % catalyst.

[e] 0.5 mol % catalyst.

Table 3

Catalyst recycling.



Cycle	Time(h)	Yield[a] (%)	dr[b]	ee[c] (%)
1st	12	88	>98:2	>98
2nd	15	91	>98:2	>98
3rd	25	80	98:2	>98

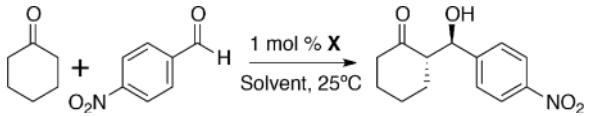
[a] Isolated yield.

[b] The diastereomeric ratios were determined by ^{1}H-NMR of the crude product.

[c] The ee values were determined by HPLC using a Chiralpak AD column.

Table 4

Screening catalysts



Entry	X	Solvent	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**	H_2O	12	96	>98:2	>98
2	**1b**	H_2O	12	98	>98:2	>98
3	**1c**	H_2O	13	99	>98:2	>98
4	**1d**	H_2O	12	98	>98:2	>98
5	**1e**	H_2O	12	97	>98:2	>98
6	**2a**	H_2O	90	87	95:5	>98
7	**2b**	H_2O	90	71	94:6	98
8	**3**	H_2O	13	93	98:2	>98
9	**1f**	H_2O	90	79	97:3	>98
10	**2c**	H_2O	90	43	93:7	98
11	**1a**[d]	Toluene	16	98	95:5	97
12	**1a**[d]	Toluene	16	94	95:5	96
13	**2a**[d]	Toluene	16	90	95:5	89

[a] Isolated yield.

[b] dr values were determined by crude product NMR.

[c] ee values were determined by HPLC using a Chiralpak AD column.

[d] 10 mol % catalyst.

Table 5

Gibbs Free energies of transition structures for the aldol addition step relative to isolated reactants and organocatalyst (kcal/mol)[a]

	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$ (1a – 1f)
TS-**1a**$_{vacuum}$	34.6	0.2
TS-**1f**$_{vacuum}$	34.4	—
TS-**1a**$_{water}$	24.7	−2.6
TS-**1f**$_{water}$	27.3	—

[a]The geometries were fully optimized by M06-2X/6-31G(d) in vacuum or using the SMD model to account for the solvation effect of water.