# Efficient direct asymmetric aldol reactions in water using chiral diamide as organocatalysts

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**Abstract.** Two chiral diamide organocatalysts, N,N'-(oxybis(4,1-phenylene))bis(pyrrolidine-2-carboxamide) (IVa) and N,N'-(methylenebis(4,1-phenylene))bis(pyrrolidine-2-carboxamide) (IVb), were developed to catalyze asymmetric aldol reactions in water with low catalyst loadings ranging from 30% to 10%. This study aimed to evaluate the influence of chiral concavity of oxygen bridge catalyst IVa on the transition state of aldol reaction in water compared to methylene bridge catalyst IVb in terms of diastereoselectivity, optical purity, reaction time and catalyst loading. The reaction conditions were optimized using p-nitrobenzaldehyde as acceptor and cyclohexanone as donor in the aldol reaction. Oxygen-bridged catalyst IVa showed superior performance to catalyst IVb in water, achieving a reaction time of 28 h, a diastereoselectivity ratio of 78:22 (anti/syn), and an enantiomeric excess of up to 97%. This effect was attributed to

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the assembly of a chiral cavity facilitated by hydrogen bonds at the oil– water interface and the proximity of the catalytic sites favored by the oxygen bridge of catalyst IVa. Organic solvents, such as DMSO, DCM, and hexane, offered excellent diastereoselectivity, but had reaction times four times longer than those in water. This study highlights the potential of organocatalyst IVa for environmentally friendly asymmetric aldol reactions.

**Key words.** Chiral proline-Amide, Aldol Reaction, chiral concavity, Organocatalysis, Oxygen-Rich Catalyst, Catalytic Transition State.

## 1. Introduction

Since the groundbreaking work conducted by List et al in 2000[1-2], The application of small organic compounds as catalysts has attracted considerable interest. Following these seminal studies, the field of organocatalysis experienced a remarkable surge in research intensity.

Examination of organocatalysts in aqueous environments represents a promising domain of inquiry for the development of sustainable and efficient techniques for organic synthesis. Traditional organocatalyzed reactions have typically been conducted in organic solvents, such as dichloromethane, tetrahydrofuran (THF), and toluene. The use of water as a solvent offers several advantages, particularly environmental sustainability, safety, and affordability [3].

influence of water interactions: disruptive ionic, hydrogen bonding, and hydrophobic interactions on C-C bond forming reactions [4], inspired by the success of natural enzymes such as aldolases and antibodies, which accelerate these reactions in water [5–7].

Recent studies have made substantial advancements in refining the structure of l-proline to improve its catalytic efficiency [8,9]. These breakthroughs have enabled the use of novel, highly modified proline-based organocatalysts for a wide range of organic transformations, including small peptides, proline thioamides, and ionic liquid-tagged prolines. Despite considerable efforts to create catalysts with broad applicability, the development of asymmetric organic reactions in water using minimal amounts of catalyst remains a highly sought-after goal in the field of synthetic chemistry [3].

The synergy between acidic and basic properties is essential for the creation of cooperative catalysts13. These principles are applicable to the development of asymmetric metal catalysts and organocatalysts [10–12]. Chiral ligands have been used successfully in several organocatalytic reactions.

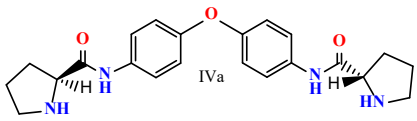
The concept of chiral catalytic pockets in C2-symmetric organocatalysts has been investigated. This pocket aims to create a spatially defined environment that improves the ability of the catalyst to promote specific reactions and favors the formation of a particular product [13–16]. Some studies have suggested that hydrogen bonding at the oil-water interface plays a role in the assembly of this pocket [3]. Delaney et al. contributed to this field by synthesizing novel C2-symmetric organocatalysts that enable direct asymmetric reactions in water, highlighting the significance of these catalysts in modern asymmetric synthesis. They demonstrated that the proximity of the catalytic sites in these organocatalysts is essential for promoting specific reaction pathways and the formation of products with high enantioselectivity [3,17].

Based on previous research [13,17–20], we hypothesized that the prolinamide organocatalyst with its chiral concavity at the oil-water interface would affect the chiral assembly process. Additionally, we aimed to investigate the impact of using an

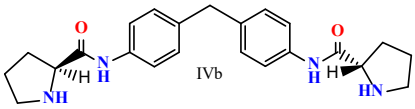
oxygen-rich catalyst on this process via hydrogen bonding in oil-water.

To test this hypothesis, we synthesized two organocatalysts, N,N'-(oxybis(4,1-phenylene))bis(pyrrolidine-2-carboxamide) IVa and N,N'-(methylenebis(4,1-phenylene))bis(pyrrolidine-2-carboxamide) IVb, both of which feature two proline amide units; the first is joined by oxydibenzene and the second by diphenyl methane.

The primary aim of this study was to assess the efficacy of concavity chiral organocatalysts with multiple amide units and determine the influence of the oxygen-rich catalyst IVa in the transition stage of the water-aldol reaction compared to IVb (Figure 1) with respect to the optical purity of the aldol reaction. This was achieved through an aldolization reaction involving para-nitrobenzaldehyde and a 3-fold excess of cyclohexanone. In this study, we examined several experimental variables, including the reaction time, temperature, optical and chemical yields, catalyst loading, solvents, and recyclability of the catalyst. Finally, organocatalysts IVa and IVb (Figure 1) were compared in terms of aldol reactions in water, solvents, and neat conditions.




(2*S*,2'*S*)-*N*,*N*'-(oxybis(4,1-phenylene))bis(pyrrolidine-2-carboxamide)




(2*S*,2'*S*)-*N*,*N*'-(methylenebis(4,1-phenylene))bis(pyrrolidine-2-carboxamide)

**Fig. 1.** Bifunctional prolinamides derived from 4,4'-oxybisbenzenamine and 1,1'-biphényl-4,4'-diamine.

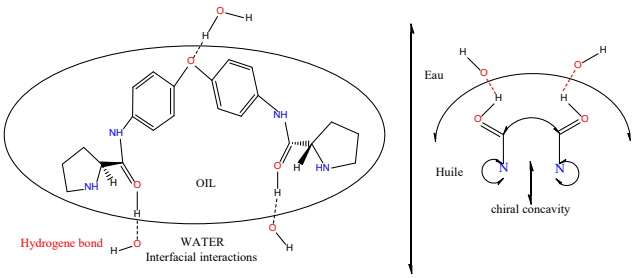
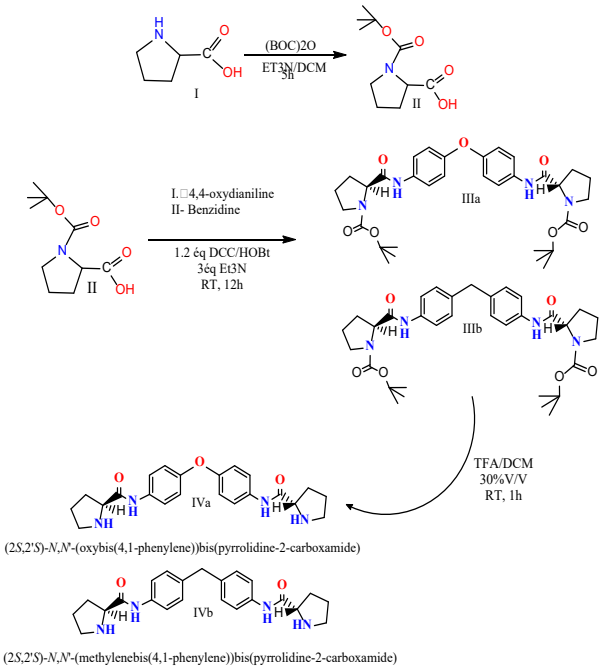



**Fig. 2.** propose catalytic conformation adopted by C2-symmetrique organocatalysts

## 2. Results and discussion:

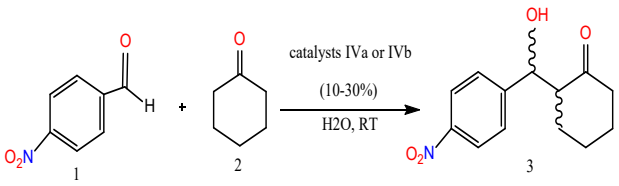
The organocatalysts were successfully prepared via a three-step synthesis using affordable starting materials (Scheme 1). The process began with the N-protection of the L-proline-amine derivative (compound I) using Boc2O, yielding compound II in a high yield (82%). Following established procedures from the literature [21], the second step involved tethering the protected proline unit to each end of the diamine using 4,4-oxydianiline as Catalyst IVa and benzidine as Catalyst IVb via DCC-, HOBt-, and Et3N-mediated peptide coupling, resulting in the formation of bis-prolinamides IIIa and IIIb. Finally, the Boc protecting group was selectively removed using a solution of 30% v/v trifluoroacetic acid (TFA) in dichloromethane. The resulting crude products were then neutralized with a saturated sodium bicarbonate solution and dried to yield the pure organic catalysts IVa and IVb.




**Scheme.1.** Synthesis of Chiral Organocatalysts Iva and IVb

## 2.1.Optimization of the reaction conditions

Two specific reactions were investigated to assess the performance of catalysts IVa and IVb (Scheme 2). In these reactions, p-nitrobenzaldehyde (1) served as the acceptor molecule and cyclohexanone (2) as the donor molecule for the aldol reaction. The reaction conditions were optimized with a low catalyst loading of 10 mol% in pure water at room temperature, which resulted in the efficient formation of the desired 1,2-addition product (3) in a high yield within a short reaction time (Table 1).




**Scheme2.** Catalyzed Aldol Reaction using a Symmetric Organocatalyse Iva and IVb

**Table 1.** Performance Comparison of Catalysts IVa and IVb in Direct Aqueous Aldol Reactions (10%)[a].

| Entry | Catalyst IVa/IVb | Load% | Conv (%) | Time | dr % (anti/syn)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | IVa | 10% | 100% | 56h | 78/22 | 97 |
| 2 | IVb | 10% | 87% | 80h | 77/23 | 95 |

[a] Catalyst IVa (30 mol %), 1 ml solvent, cyclohexanone (1.98 mmol, 3eq), p-nitrobenzaldehyde (0.66 mmol) Mixed and stirred at RT for a defined period.[b] RMN analysis of the crude product revealed the diastereomeric ratio (dr).[c]Chiralpak AD Column Reveals Enantiomeric Excess (ee). The separation was performed using a 1:9 mixture of 2-propanol and n-hexane at a flow rate of 1 mL/min.

With catalyst IVa, the anti-3 aldol product was obtained with complete conversion, high enantiopurity (97% ee), and an excellent diastereomeric ratio of 77/23 (anti/syn) within 56 h. In contrast, catalyst IVb afforded 87% yield with similar enantiopurity (95% ee) and diastereoselectivity (77/23 anti/syn), but required twice as long (80 h) to complete the reaction (Table 1, entry 2). This significant difference in reaction time is attributed to the presence of an oxygen atom at the symmetry center of catalyst IVa, which facilitates the formation of an additional hydrogen bond, supplementing the two hydrogen bonds formed by the diprolinamide units present in both catalysts.

**Table 2.** Performance Comparison of Catalysts IVa and IVb in Direct Aldol Reactions (10%) under dry conditions.[a]

| Entry | Catalyst IVa/IVb | Load% | Conv (%) | Time | dr % (anti/syn)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | IVa | 10% | 94% | 78h | 77/23 | 86 |
| 2 | IVb | 30% | 96% | 56h | 60/40 | 94 |

[a] Catalyst IVa (30 mol %), 1 ml solvent, cyclohexanone (1.98 mmol, 3eq), p-nitrobenzaldehyde (0.66 mmol) Mixed and stirred at RT for a defined period.[b] RMN analysis of the crude product revealed the diastereomeric ratio (dr).[c] Chiralpak AD Column Reveals Enantiomeric Excess (ee). The separation was performed using a 1:9 mixture of 2-propanol and n-hexane at a flow rate of 1 mL/min.

To demonstrate the effectiveness of catalysts IVa and IVb in aqueous media, we investigated their catalytic activity under the same conditions without water. Table 2 summarizes the results of the aldol reaction with 10% catalyst loading. Catalyst IVa displayed 96% conversion within 78 h with excellent enantiopurity (dr 77/23, ee 97%) (Table 2, entry 1). In contrast, catalyst IVb required over 100 h to achieve 60% conversion, exhibiting a noticeable decrease in diastereoselectivity (dr 65/35); however, the enantioselectivity was good (ee 94%) compared to that of cataltyst IVa (Table 2, entry 1-2). Consequently, catalyst IVa was twice as fast as catalyst IVb in terms of reaction time. In addition, the diastereoselectivity of catalyst IVa was superior with catalyst IVa that of catalyst IVb (Table 2, entries 1 and 2), although catalyst IVb demonstrated excellent enantioselectivity.

We compared the performance of catalysts IVa and IVb in two scenarios: in aqueous media and under dry conditions. Both catalysts worked well in water, achieving high conversion rates, fast reaction times, and good control over product stereoisomers (diastereoselectivity and enantioselectivity) (Table 1, entry 1; Table 2, entry 1). However, a key difference emerged: catalyst IVa was significantly faster than IVb in

water (table 1-2 entry 1-2). It achieves a total conversion rate in less time and with slightly better control over the specific stereoisomer of the product.

Water significantly enhanced the performance of both catalysts. However, catalyst IVa thrives in this environment, being twice as fast as catalyst IVb. This reinforces our initial theory on the influence of water interactions and catalyst site proximity on the stereoselectivity of the reaction.

**Table 3.** Impact of catalyst amount: evaluating IVa performance in aqueous and solvent-Free Aldol Processes [a].

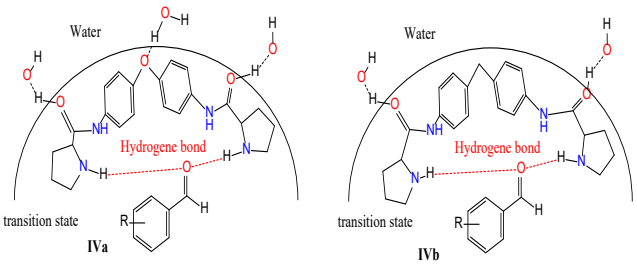
| Entry | H2O/ Neat | Load % | Conv (%) | Time | dr % (anti/syn)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | H2O | 30% | 100% | 28h | 69/31 | 97 |
| 2 | Neat | 30% | 96% | 56h | 60/40 | 85 |
| 3 | H2O | 10% | 100% | 56h | 78/22 | 97 |
| 4 | Neat | 10% | 94% | 78h | 75/25 | 86 |

[a] Catalyst IVa (30 mol %), 1 ml solvent, cyclohexanone (1.98 mmol, 3eq), p-nitrobenzaldehyde (0.66 mmol) Mixed and stirred at RT for a defined period.[b] RMN analysis of the crude product revealed the diastereomeric ratio (dr).[C] Chiralpak AD Column Reveals Enantiomeric Excess (ee). The separation was performed using a 1:9 mixture of 2-propanol and n-hexane at a flow rate of 1 mL/min.

Table 3 displays the results of the aldolization reaction using oxygen-rich catalyst IVa with loadings of 10% and 30% under both aqueous and dry conditions. The catalytic activity was twice as fast with 30% loading compared to 10% loading, as indicated by the reaction times (Table 3, Entries 1 and 3). Additionally, diastereoselectivity was higher at 10% loading than at 30% loading (entries 1 and 3, Table 3). Notably, the enantioselectivity decreased from 97% in water to 86% in the absence of water, regardless of whether the loading was 10 or 30% (entries 1 and 2, Table 3).

Overall, aldolization reactions using the oxygen-rich catalyst IVa in water consistently showed more favorable results in

terms of conversion rates, diastereomeric ratios, and enantiomeric excesses than reactions under pure conditions.
This advantage is likely due to the strategic placement of an oxygen atom. This oxygen serves a dual purpose. First, it enhances the water solubility through hydrogen bonding, which accounts for IVa faster performance of IVb in aqueous environments. Second, oxygen facilitates the formation of a favorable chiral concavity due to the proximity of the catalytic sites, which improves the spatial arrangement and likely contributes to IVa higher catalytic activity of IVb (Scheme 3).




**Schema 3:** Origin of Chirality: A Look at the Proposed Transition State for Iva/IVb-Mediated Enantioselective Aldol Reaction.

The proposed transition state benefits from the symmetrical arrangement of the catalyst units. This symmetry ensures that both catalyst units are equally close to the incoming aldehyde molecule. This proximity allows for a high concentration of the activated chiral enamine intermediate, which boosts reaction efficiency.
From the chirality perspective, this symmetry is crucial. This ensured that each enamine reacted with the correct side (Re or Si) of the incoming aldehyde. This selective reaction resulted in enrichment of the observed product in one enantiomer. The key to this selectivity was the formation of a temporary chiral pocket around the reactants by the catalyst.
However, if the two catalyst units move apart, this "proximity advantage" weakens. As the distance between the catalyst and aldehyde increases, their likelihood of working together effectively diminished [18].

The significance of water in these reactions has been emphasized in research conducted by Pedrosa et al. [9,22]. These researchers proposed a transition-state model for an organocatalyzed aldol reaction in water in which a prolinamide with multiple amide groups plays a crucial role. This model suggests that each amide group can function in one of two ways: either as a hydrogen bond acceptor, helping to organize the reaction at the interface between water and organic molecules, or as a hydrogen bond donor, enabling precise positioning of the incoming aldehyde molecule. The concept of multiple hydrogen-bond donors facilitating highly stereochemical aldol reactions is not novel, as demonstrated by Gong et al [23]. These findings collectively emphasize the critical role of water in promoting chiral induction and enhancing the catalytic activity in aldol reactions utilizing chiral diamines as organocatalysts.

After studying the efficiency of the concave prolinamlide organocatalysts in water and in neat conditions, we tested the catalytic activity of the Iva catalyst with 30% loading in organic solvents using a direct asymmetric aldol reaction as the reaction model (Table 3).

**Table 4.** Effect of solvent selection on direct asymmetric aldol reactions with catalyst IVa at 30% charge[a].

| Entry | Solvent | Time | Conversion (%) | dr% (anti/syn)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | Hexane | 48h | 100% | 54/46 | 94 |
| 2 | DCM | 96h | 96% | 71/29 | 100 |
| 3 | DMSO | 96h | 65% | 60/40 | 98 |

[a] Catalyst IVa (30 mol %), 1 ml solvent, cyclohexanone (1.98 mmol, 3eq), p-nitrobenzaldehyde (0.66 mmol) Mixed and stirred at RT for a defined period.[b] NMR analysis of the crude product revealed the diastereomeric ratio (dr).[c] Chiralpak AD Column Reveals Enantiomeric Excess (ee). The separation was performed using a 1:9 mixture of 2-propanol and n-hexane at a flow rate of 1 mL/min.

The results of the direct aldol reaction in nonpolar solvents such as hexane and dichloromethane (DCM) demonstrated

diastereomeric ratios ranging from 54:46 to 71:29 (Table 3, entries 1-2), with aldol product 3 conversion rates ranging from 96% to 100%. The primary product, anti-3, was obtained with an enantiomeric excess ranging from 94 to 100%, while the aldol reaction using dichloromethane was twice as long as that using hexane (Table 4, entries 1-2). In contrast, the aldol reaction in the polar solvent N,N-dimethyl sulfoxide (DMSO) yielded a 65% conversion rate, a diastereomeric ratio of 60:40, and an enantiomeric excess of 99% (Table 4, entry 3).

The DCM-catalyzed aldolization afforded an enantiomerically pure product (ee 100%) with excellent diastereoselectivity in hexane. The diastereoselectivity was moderate to good in DMSO, but the enantioselectivity was still excellent, as shown by entries 1-3 Table 4.

In contrast to the kinetics observed in aqueous solutions, the aldolization reaction in organic solvents such as hexane, dichloromethane (DCM), and dimethyl sulfoxide (DMSO) is typically longer, lasting two to three times longer. It can be deduced that the Iva catalyst exhibits exceptional catalytic performance in water, with short reaction times, complete conversion, noteworthy diastereoselectivity, and excellent enantioselectivity in water, with and without solvent.

## 3. Conclusion:

In conclusion, we successfully synthesized two prolinamide organocatalysts, IVa and IVb, which were distinguished by the presence of an oxygen atom on the symmetry axis of IVa. Each catalyst was evaluated for its ability to facilitate the asymmetric aldolization reaction in water without additives, by optimizing the experimental conditions. The catalytic activity in water gave the best results compared to the reactions without water or in the presence of an organic solvent, which can be explained by the effect of intramolecular interactions between the prolinamide units, favoring a cooperative catalytic process. In addition, the steric environment created by the concave exerts conformational effects, leading to alcohols

with high optical purity and high yield. The presence of oxygen in the symmetry axis of IVa increased its catalytic power compared to that of IVb. The results indicate that IVa is twice as efficient as IVb because of the hydrogen bonding interactions at the oil-water interface and the effect of the chiral pocket on improving the optical purity.

Interestingly, addition of lipophilic groups to improve the efficiency of organocatalysts is a promising strategy. Modifying the structure of catalysts to promote the alignment of molecules along the oil-water interface through specific interactions, such as hydrogen bonds, could lead to improved aldolization reactions in water [3,21–23].

This approach could potentially further optimize the efficiency and selectivity of reactions catalyzed by these compounds.

However, research on the use of concave chiral prolinamines as organocatalysts for efficient and selective aldol reactions in water has provided new perspectives in the field of asymmetric catalysis. These results highlight the importance of water in promoting chiral induction and catalytic activity as well as the impact of hydrogen bonding interactions at the oil-water interface.

This strategy warrants further investigation for the development of highly efficient and selective catalysts.

## 4. Experimental section:

### General

Both Benzaldehyde derivatives and cyclohexanone were obtained from commercial suppliers. 1H and 13C NMR spectroscopy was performed at room temperature using a high-performance Jeol spectrometer operating at 500 MHz for protons and 500.13 MHz for carbons. The positions of the NMR signals were reported in ppm relative to the tetramethylsilane (TMS) standard reference compound. The solvent peak served as the internal reference for each measurement. Specific reference values for commonly used

solvents (chloroform-d, CDCl3, dimethyl sulfoxide-d6, and DMSO-d6) are provided for both 1H and 13C NMR spectroscopy.

High-Resolution Mass Spectrometry was used to determine the precise molecular weight of the compounds. The analysis employed Electrospray ionization (ESI) coupled with time-of-flight (TOF) mass spectrometry in positive ion mode. The instrument's mass range was extended from 50 to 3000 Daltons (Da), and calibrations (both external and internal) were performed using an electrospray calibrant solution. The optical activity of the compounds was measured using a polarimeter. Prior to the analysis, the instrument was calibrated with a pure solvent to establish a baseline. IR spectra were acquired using a Perkin–Elmer instrument to gather additional structural information on the molecules.

The reactions were monitored and the purity of the isolated products was assessed using thin-layer chromatography (TLC) on Merck silica gel plates. The synthesized compounds were purified by separation on columns packed with silica gel. A high-performance liquid chromatography (HPLC) system equipped with specialized chiral stationary phase columns (Chiralpak AD) was used to determine the enantiomeric purity (ee) of the desired product.

All the newly synthesized compounds were comprehensively characterized using 1H NMR, 13C NMR, and HRMS techniques. For previously known compounds, confirmation was achieved by comparing the 1H and 13C NMR data with existing information.

### 4.1. N,N'-(tertiobutyloxybis(4,1phenylene))bis(pyrrolidine-2-carboxamide) (IIIa)

4,4'-Oxydianiline (1 equivalent, 10 mmol, 2 g) was dissolved in dry dichloromethane (DCM, 60 mL). Subsequently, N-Boc-L-Proline (2.2 equivalents, 22 mmol, 4.3 g), HOBt (2.2 equivalents, 22 mmol, 2.97 g), and DCC (2.2 equivalents, 22 mmol, 4.53 g) were added to the solution. The reaction

mixture was cooled in an ice bath to 0°C and triethylamine (6 equiv, 60 mmol, 8.36 g) was added dropwise. The reaction mixture was agitated at 0°C for 15 min and stirred at room temperature for 12 h. The resulting crude reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and acidified with saturated citric acid solution. The mixture was neutralized with 10% NaHCO3 and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous Na2SO4, and the solvent was removed using a rotary evaporator to yield compound IVa as a syrup (4.2 g, 71.18% yield, respectively). The crude product was purified by column chromatography using a mixture of ethyl acetate/hexane (1/2) for subsequent steps.

δ 1H RMN (500 MHz, DMSO-d6): 9.91 (S, 1H), 7.57 – 7.51 (m, 2H), 6.90 (t, 2H), 4.17 – 4.10 (m, 1H), 3.41 – 3.32 (m, 2H), 2.16 (dd, 2H), 1.87 – 1.78 (m, 2H), 1.25(S, 9H).
FTMS+ pESI fullMS: calculated for C32H42N4O7: C, 64.63; H, 7.12; N, 9.42; O, 18.83 M= 595.31; found: M= 595.18.

### 4.2. N,N'-(oxybis(4,1-phenylene))bis(pyrrolidine-2 carboxamide) (IVa)

Compound IIIa (4.2 g, 10 mmol) was then dissolved in dry dichloromethane (15 mL). Trifluoroacetic acid (5 mL), a strong acid, was added dropwise while maintaining the temperature at 0°C. This step removes the Boc protecting group from the amino acid unit in IIIa, creating the desired product IVa. The acid concentration was controlled at 30% by volume, relative to DCM. The mixture was stirred for 15 min at 0°C, followed by stirring for an additional hour at room temperature. The solvent was then removed using a rotary evaporator. The residue was then basified with a saturated sodium bicarbonate solution until the pH reached 8-9. Product IVa was extracted from the aqueous mixture using chloroform (repeated three times with 10 mL portions each). The organic

layer containing the product was washed with water and brine to remove any water-soluble impurities. Finally, the organic extract was dried using anhydrous sodium sulfate and the remaining solvent was evaporated using a rotary evaporator to yield compound IVa as a yellow viscous oil.
δ 1H RMN (500 MHz, DMSO-d6) δ 9.91(S,1H), 7.52 (d, 2H), 6.68 (d, J = 8.2 Hz, 2H), 3.74(S, 1H), 2.93 – 2.84 (m,2H), 2.03 (d, 2H), 1.83 (m, 1H), 1.66 – 1.61 (m, 2H).
FTMS+ pESI full ms: calculated for C22H26N4O3: C, 66.99; H, 6.64; N, 14.20; O, 12.17 395.20; found:395.18.

### 4.3. N,N'-(tertiobutyl-methylenebis(4,1 phenylene)) bis (pyrrolidine-2-carboxamide) (IIIb)

A solution of 4,4'-diaminobiphenyl (1 equiv, 10 mmol, 1.8 g) in dry dichloromethane (DCM, 60 mL) was prepared and stirred. Next, N-Boc-L-Proline (2.2 equivalents, 22 mmol, 4.3 g), HOBt (2.2 equivalents, 22 mmol, 2.97 g), and DCC (2.2 equivalents, 22 mmol, 4.53 g) were added to the solution. The mixture was brought to 0°C and triethylamine (6 equiv, 60 mmol, 8.36 g) was slowly added while stirring vigorously for 15 min at 0°C. and was incubated for 12 h at room temperature. The crude product was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the resulting mixture was acidified with a saturated solution of citric acid. The acidified mixture was neutralized with 10% NaHCO3 and extracted using ethyl acetate. Organic extracts were pooled and rinsed with water and brine. They were then dehydrated using anhydrous sodium sulfate and the solvent was removed using a rotary evaporator to yield compound IVB as a syrup (4.2 g, 71.18% yield).
δ 1H RMN (500 MHz, DMSO-$d_6$): 10.01(S,1H), 7.64 (d, *2H*), 7.57 (d, 2H), 4.17 (dd, *1H*), 3.39 (dt,2H), 2.21 – 2.07 (m, 2H), 1.87 – 1.83 (m, 2H), 1.68 (dd,*2H*), 1.24 (S,9H).
FTMS+ pESI full MS: calculated for C33H44N4O6: C, 66.87; H, 7.48; N, 9.45; O, 16.20 M= 593.33; found: M= 593.40.

### 4.4. N,N'-(methylenebis(4,1-phenylene))bis(pyrrolidine-2-carboxamide) (IVb)

Compound IIIb (4.2 g, 10 mmol) was dissolved in dry dichloromethane (5 ml) and trifluoroacetic acid (5 ml) was added dropwise at 0°C. The reaction mixture was agitated for 15 min at 0°C, and then for 1h at room temperature. The mixture was concentrated under vacuum and basified with a saturated solution of NaHCO3 (pH= 8-9. The product was extracted using chloroform (3 × 10 ml), washed with water and brine, and dried over anhydrous Na2SO4. The solvent was removed using a rotavapor to obtain compound IVa as viscous oil.

δ 1H RMN (500 MHz, Methanol-$d_4$): 8.45 (S,1H), 7.47 (m, 2H), 7.33 (d, 2H), 4.99 (S, 1H), 4.00 (d, 1H), 3.14 (d, 2H), 2.73(S, 2H), 1.84 – 1.83 (m, 1H), 1.30 – 1.22 (m, 2H).
FTMS+ pESI full MS: calculated for C23H28N4O2: C, 70.38; H, 7.19; N, 14.27; O, 8.15; 393.19; found: 393.22.

## 5. General experimental procedure for aldol reaction

### 5.1. Reaction in water:

Organocatalysts IVa-IVb (30 mol%-10 mol%) were dissolved in 1 mL of water and combined with cyclohexanone (0.310 mL, 3 mmol) for 10 min. Subsequently, 4-nitrobenzaldehyde (0.05 g, 0.33 mmol) was added, and the reaction mixture was stirred vigorously at room temperature for the specified duration. The progress of the reaction was monitored using thin-layer chromatography (TLC) to ensure full conversion. Once the reaction was complete, the emulsion was extracted with CHCl3 (2 × 10 mL) and the organic phase was washed with 10% citric acid (10 mL). The organic phase was dried over Na2SO4 and the solvent was evaporated under vacuum to yield the crude aldol product as a yellow solid. The product was purified by flash column chromatography on silica gel using a blend of hexane and ethyl acetate in a ratio of 3:1. The

desired product, reaction conversion, and diastereomeric ratios were determined by 1H NMR spectroscopy. Enantiomeric excess was determined by HPLC using a Chiralpak AD column with as the mobile phase of hexane/2-propanol.

### 5.2. The reaction under free solvent conditions

Organocatalysts IVa-IVb (30 mol%-10 mol%) were combined with cyclohexanone (0.310 mL, 3 mmol) and stirred for 10 min. Following this, 4-nitrobenzaldehyde (0.05 g, 0.33 mmol) was added, and the reaction mixture was agitated vigorously at ambient temperature for the designated time period. The progress of the reaction was monitored using TLC to ensure complete conversion. Upon completion, the emulsion was extracted with chloroform (2 × 10 mL) and the resulting organic layer was rinsed with 10% citric acid solution (10 mL). The organic layer was dehydrated using sodium sulfate and the solvent was removed under vacuum to obtain the crude aldol product, which appeared as a yellow solid. The product was purified by flash column chromatography on silica gel using a blend of hexane and ethyl acetate in a ratio of 3:1. The desired product, reaction conversion, and diastereomeric ratios were assessed by 1H NMR spectroscopy. The enantiomeric excess was determined by HPLC using a chiral column (Chiralpak AD) with hexane/2-propanol as the mobile phase.

### 5.3. Reactions with different solvents

The following procedure illustrates the reaction of cyclohexanone with p-nitrobenzaldehyde (2a) in various solvents (DCM, Hexane, DMSO) using catalyst IVa.
Thin-layer chromatography (TLC) (organocatalyst IVa (30 mol%, 0.072 g) was dissolved in 1 mL of the chosen solvent (DCM/hexane/DMSO) and mixed with cyclohexanone (0.310 mL, 3 mmol) for 10 min. Subsequently, 4-nitrobenzaldehyde (0.05 g, 0.33 mmol) was added, and the mixture was agitated vigorously at ambiante temperature for the specified duration. Thin layer chromatography (Thin layer chromatography

(TLC) was used to monitor the progress of the reaction to ensure complete conversion. After completion, the mixture was extracted with chloroform (2 × 10 mL) and the organic layer was subsequently treated with 10% citric acid solution (10 mL). The organic phase was dried over Na2SO4 and the solvent was evaporated under vacuum to yield the crude aldol product as a yellow solid. The product was purified by flash column chromatography on silica gel using a blend of hexane and ethyl acetate in a ratio of 3:1. The desired product, along with reaction conversion and diastereomeric ratios, was analyzed by 1*H* NMR spectroscopy. Enantiomeric excess was determined by HPLC using a Chiralpak AD column with hexane/2-propanol as the mobile phase.

### 5.4. Reactions with different aldehyde fonctions:

Thin-layer chromatography organocatalyse IVa (30 mol%, 0.072 g) was dissolved in 1 mL of water and combined with cyclohexanone (0.310 mL, 3 mmol) for 10 min. Subsequently, different aldehydes (0.33 mmol) (as listed in Table 4) were added, including 4-nitrobenzaldehyde (0.05 g, 0.33 mmol). The mixture was vigorously agitated at the ambient temperature for a specified period. Thin layer chromatography (TLC) was used to monitor the progress of the reaction to ensure complete conversion. Upon completion, the mixture was extracted with CHCl3 (2 × 10 mL) and the organic layer was washed with 10% citric acid (10 mL). The organic layer was then dried over Na2SO4 and the solvent was evaporated under vacuum to yield the crude aldol product as a yellow solid. The product was purified by flash column chromatography on silica gel using a blend of hexane and ethyl acetate in a ratio of 3:1. The desired product, along with the reaction conversion and diastereomeric ratios, was analyzed by 1 H NMR spectroscopy. Enantiomeric excess was determined by HPLC using a Chiralpak AD column with hexane/2-propanol as the mobile phase.

## 6. Results:

### 6.1. (S)-2-((R)-Hydroxy(4-nitrophenyl)methyl) cyclohexanone

IR film anti-3: 3506 cm-1, 2934 cm-1, 1690 cm-1, 1519 cm-1, 1344 cm-1

δ 1H RMN (500 MHz, Chloroform-d): 8.21 – 8.18 (m, 2H), 7.51 – 7.48 (m, 2H), 4.92 – 4.85 (m, 1H), 4.14 – 4.00 (m, 1H), 2.62 – 2.56 (m, 1H), 2.52 – 2.49 (m, 1H), 2.41 – 2.35 (m, 1H), 2.12 – 2.09 (m, 1H), 1.85 – 1.79 (m, 1H), 1.74 – 1.70 (m, 1H), 1.67 – 1.64 (m, 2H), 1.42 – 1.35 (m, 1H).

FTMS- pESI full ms: calculated for C13H15NO4: C, 62.64; H, 6.07; N, 5.62; O, 25.67; 248.10 ; found: 248.09.

HPLC analysis: Chiralpak AD (hexane/i-PrOH = 90:10, 1.0 mL/min, 254 nm, 25 °C): tminor = 22.6 min, tmajor = 30.9 min, and ee = 95%.

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