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-Graphical Abstract

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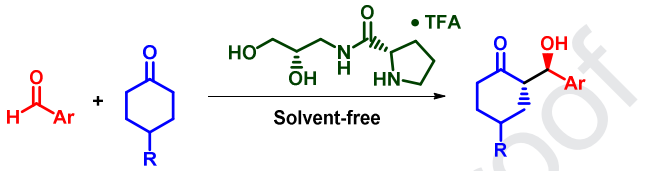

- Preparation of four novel organocatalysts
- Solvent-free protocol
- *o*-, *m*- and *p*-substitued aryl groups
- Up to three new stereocenters in a single step
- 16 examples
- Up to 95% yield
- Up to 19:1 d.r. and 98% e.e.

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Design and Preparation of a Novel Prolinamide-based Organocatalyst for the Solvent-free Asymmetric Aldol Reaction

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ABSTRACT

The preparation of four novel organocatalysts as highly diastereo and enantioselective catalysts for the solvent-free asymmetric aldol reaction was described. These organocatalysts were synthesized in eight steps applying simple and commercially available starting materials. The best results were obtained for the proline-derived catalyst, providing access to the desired adducts in up to 95% yield, 1:19 *syn*/*anti* and 98% e.e. Moreover, even sterically bulky aldehydes and substituted cyclohexanones were well tolerated. DFT calculations and control experiments indicated that several hydrogen bonding interactions between the aldehyde and the enamine intermediate are responsible for the stereoselective chiral induction process and that the trifluoroacetate counter-anion is crucial for the attainment of higher stereoselectivities.

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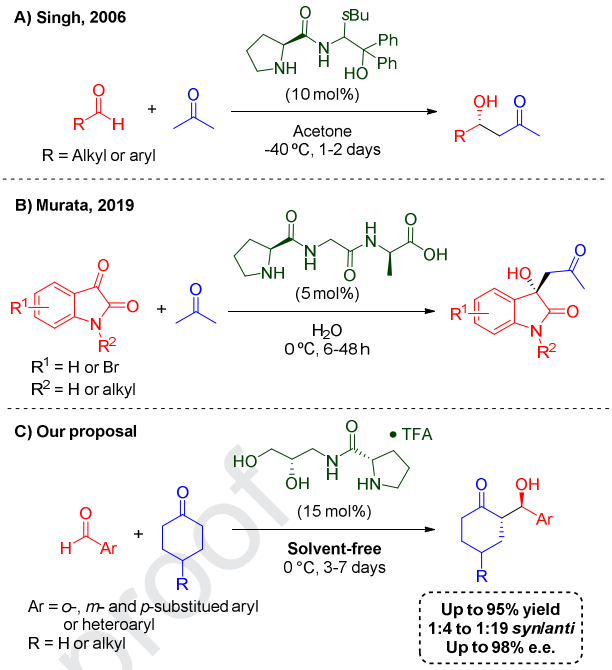
1. Introduction

Reactions involving the formation of carbon-carbon bonds have always attracted great interest in the organic chemistry community [1]. Over the last few years, with the great development of the asymmetric organocatalysis field, elegant protocols to those transformations were further developed, especially those involving the simultaneous formation of several stereogenic centers [2,3]. In this context, the aldol reaction appears as an important transformation in which two or even more stereocenters can be generated in a single reaction step [4]. Furthermore, the reagents (aldol acceptor and aldol donor) do not require any pre-activation step, as occurs in the Mukaiyama aldol reaction.

Asymmetric protocols for the aldol reaction have presented great developments since the pioneer studies of List and Barbas III with *L*-proline [5–7]. Thus, several catalysts were designed and applied in this transformation, including peptides [8], metal catalysts [9], thioureas [10,11], squaramides [12], and prolinamide organocatalysts [13]. On the other hand, more efficient chiral catalysts are still required for the enantioselective aldol reaction, and the development of a general protocol for this transformation is still a challenge [4].

Prolinamide organocatalysts, in the presence of ketones, are noteworthy for their capacity to form iminium/enamine intermediates. These catalysts generally allow the aldol reaction to proceed at milder reaction conditions [13]. Most of these catalysts rely on hydrogen bonding interactions for the chiral induction. For example, Singh's group described the use of a prolinamide-based organocatalyst bearing both a *gem*-diphenyl substituted side-chain and a hydroxyl group in the asymmetric aldol reaction (Scheme 1A), affording the desired adducts in moderate yields and moderate to excellent enantiomeric excesses [14]. On the other hand, only acetone was used and the reaction required considerably lower temperatures. Another interesting study was recently described by Murata and co-workers (Scheme 1B), which prepared an unnatural tripeptide bearing an *L*-proline residue for the asymmetric aldol reaction between isatins and acetone [15]. Most interestingly, the catalyst design predicted stereocontrol by the simultaneous formation of several hydrogen bonding interactions.

Our research group has recently been studying the influence of new catalysts bearing polyol moieties derived from glycerol in organic transformations, such as the Morita-Baylis-Hillman reaction [16], especially in solvent-free protocols. Thus, we envisioned that the preparation of a chiral amine with a polyol side-chain would allow its subsequent coupling with an amino acid, affording novel chiral organocatalysts with potential applications in amino-catalyzed transformations (Scheme 1C). Furthermore, the asymmetric induction by the selective stabilization of transition states through the formation of hydrogen bonding interactions might be possible due to the presence of a side-chain bearing NH and OH groups in these catalysts.

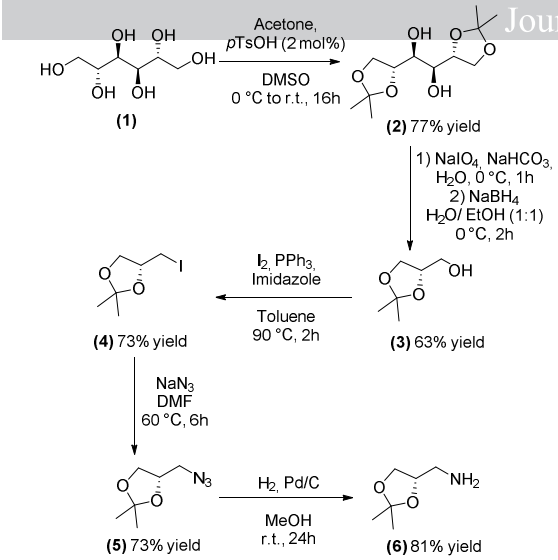


Scheme 1. Previous reports on prolinamide-catalyzed asymmetric aldol reaction and this work proposal.

2. Results and Discussion

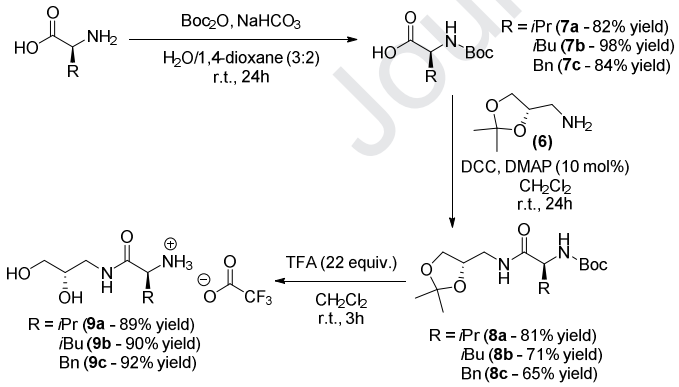
2.1. Catalysts preparation

We started our study by preparing the chiral amine **6**. This compound was prepared in five steps (21% overall yield) employing the commercially available *D*-mannitol as the initial substrate (Scheme 2). First, the hydroxyl groups were protected, affording derivative **2** in 77% isolated yield. Next, the oxidative cleavage employing sodium periodate was carried out, followed by the aldehyde reduction into the desired alcohol **3** (63% yield) using sodium borohydride. For the conversion of the hydroxyl group into the desired amine, an Appel reaction for the formation of iodide **4** (73% yield) was initially conducted, followed by a nucleophilic substitution employing sodium azide as nucleophile (73% yield) and, finally, the azide reduction through hydrogenation over palladium on carbon (81% yield). It is worth mentioning that the optical rotation of all these compounds was monitored during each reaction step and showed good agreement with the literature values.



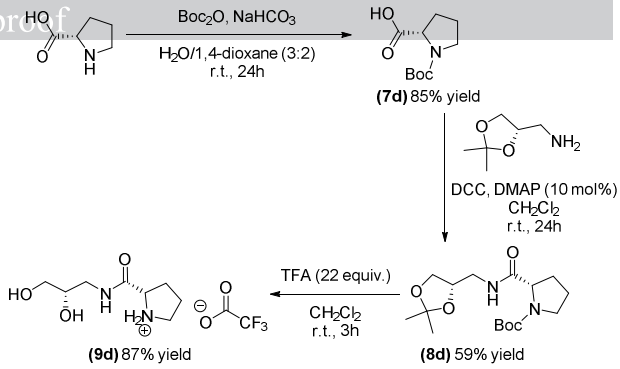
Scheme 2. Synthetic route to the chiral amine **6**.

Next, three different catalysts bearing primary amine moieties (**9a-c**) were prepared (Scheme 3). To this purpose, we initially prepared the Boc-protected amino acids **7a-c** based on literature protocols [17], prepared from the amino acids *L*-valine, *L*-leucine, and *L*-phenylalanine, respectively. This step was then followed by the *N*,*N*'-dicyclohexylcarbodiimide (DCC) mediated coupling between these protected amino acids and the previously prepared amine **6**, resulting in the desired derivatives **8a-c** in up to 81% yield. Finally, the simultaneous deprotection of the Boc and ketal groups afforded the desired catalysts **9a-c** as trifluoroacetate salts, in isolated yields between 89 and 92%. Moreover, these three-step protocol resulted in the desired products in 50-63% overall yields. The chiral purity of these catalysts and their precursors (**8a-c**) was confirmed by the ^{1}H NMR analysis of the crude reaction mixtures, which did not indicate the occurrence of epimerization during these steps.



Scheme 3. Preparation of catalysts **9a-c**.

Due to the promising results in the literature employing proline-based organocatalysts [8,13,18,19], associated with its capability to form iminium/enamine intermediates through the condensation with ketones, the preparation of the organocatalyst **9d** was carried out employing the same protocol previously applied and using *L*-proline as the initial substrate. The desired organocatalyst was isolated in 44% overall yield after the three-reaction steps, as depicted in Scheme 4.



Scheme 4. Preparation of catalysts **9d**.

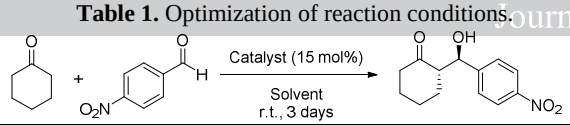
The preparation of the **salt-free 9d** catalyst was also carried out employing substrate **8d**, trichloroacetic acid (2 equiv.) under reflux for 12 hours (full details of this reaction are available in the Supplementary data). However, due the important literature precedents involving salt catalysts for the aldol reaction [20,21], we decided to continue our investigation using these compounds as trifluoroacetate salts.

2.2. Reaction optimization

The use of these novel organocatalysts in the asymmetric aldol reaction between cyclic ketones and aryl-substituted aldehydes was then studied. To this purpose, the use of these catalysts (15 mol%), employing dimethylsulfoxide (DMSO) as solvent (Table 1) at room temperature, and using 4-nitrobenzaldehyde and cyclohexanone as substrates was initially investigated. Unfortunately, the yields and the diastereomeric ratios were poor for all primary amine catalysts. On the other hand, the prolinamide-based catalyst led to a more encouraging result (entry 4). Based on literature reports employing DMSO in the presence of water as an additive (10 equiv.) [22,23], tests were also carried out in this reaction condition (entries 1-4). Although an enhancement in the stereocontrol was achieved for catalyst **9d**, the isolated yield considerably dropped.

By changing the solvent to water, although an increase in yields was detected, the stereoselectivity slightly dropped (entries 5-8). Once more, the best result was attained for the prolinamide organocatalyst. Next, tests in the absence of solvents were carried out and, surprisingly, an excellent isolated yield of 98% was obtained when employing the catalyst **9d**, with a good diastereomeric ratio (10:1) and enantiomeric excess (79%) (entry 12). It is also worth mentioning that in the absence of the catalysts no product was detected.

Table 1. Optimization of reaction conditions.

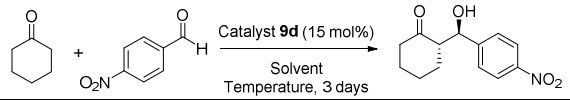


Entry	Catalyst	Solvent	Yield	d.r.[a] (*anti*/*syn*)	e.e.[b] (%)
1	**9a**	DMSO	10/25[c]	2:1/2:1[c]	ND/81[c]
2	**9b**	DMSO	9/23[c]	2:1/3:1[c]	ND/74[c]
3	**9c**	DMSO	9/24[c]	2:1/2:1[c]	ND/51[c]
4	**9d**	DMSO	72/53[c]	7:1/14:1[c]	75/87[c]
5	**9a**	H_2O	58	2:1	50
6	**9b**	H_2O	38	3:1	72
7	**9c**	H_2O	40	1:1	40
8	**9d**	H_2O	62	10:1	79
9	**9a**	-	38	1:1	38
10	**9b**	-	44	1:1	47
11	**9c**	-	77	1:1	24
12	**9d**	-	98	10:1	79

[a]Calculated through the ^{1}H NMR the analysis of the crude reaction mixture; [b]Calculated through enantiodiscriminationg HPLC; [c]Reaction carried out using 10 equiv. of water as additive. ND: Not determined.

Since the best overall results were found for the catalyst **9d**, further optimization employing this organocatalyst was carried out (Table 2). The use of polar protic (entry 1) and aprotic solvents (entry 2 and 3) failed to considerably enhance the stereoselectivity. The use of trifluoroacetic acid (TFA) as an additive (15 mol%) [24] was also evaluated, and significantly dropped the yield, d.r. and e.e. (entry 4). Interestingly, the use of catalytic TFA (15 mol%), in the absence of the catalyst **9d**, inverted the diastereocontrol towards the *syn* isomer (1:2 d.r.) (entry 5). Noteworthy, by lowering the temperature to 0 °C, in the absence of solvents and additives, the best overall reaction condition was accessed (entry 6), with 90% yield, 19:1 d.r. and 98% e.e. Finally, the catalyst loading was evaluated (entries 7 and 8) and, although similar diasteomeric ratios were obtained when using 5 or 10 mol% of organocatalyst **9d**, a considerable drop in yields and enantiomeric excesses were observed.

Table 2. Optimization of reaction conditions employing the catalyst **9d**.



Entry	Solvent/ Additive	Temperature	Yield	d.r.[a] (*anti*/*syn*)	e.e.[b] (%)
1	Methanol	r.t.	82	9:1	84
2	Toluene	r.t.	59	5:1	53
3	Dichloromethane	r.t.	90	9:1	78
4	-/TFA	r.t.	75	2:1	58
5[c]	-/TFA	r.t.	67	1:2	0
6	-/-	0 °C	90	19:1	98
7[d]	-/-	0 °C	48	15:1	72
8[e]	-/-	0 °C	73	17:1	84

[a]Calculated through the ^{1}H NMR the analysis of the crude reaction mixture; [b]Calculated through enantiodiscriminationg HPLC; [c]Reaction carried out using 15 mol% of trifluoroacetic acid in the absence of catalyst **9d**; [d]Reaction carried out employing 5 mol% of catalyst **9d**; [e]Reaction carried out employing 10 mol% of catalyst **9d**.

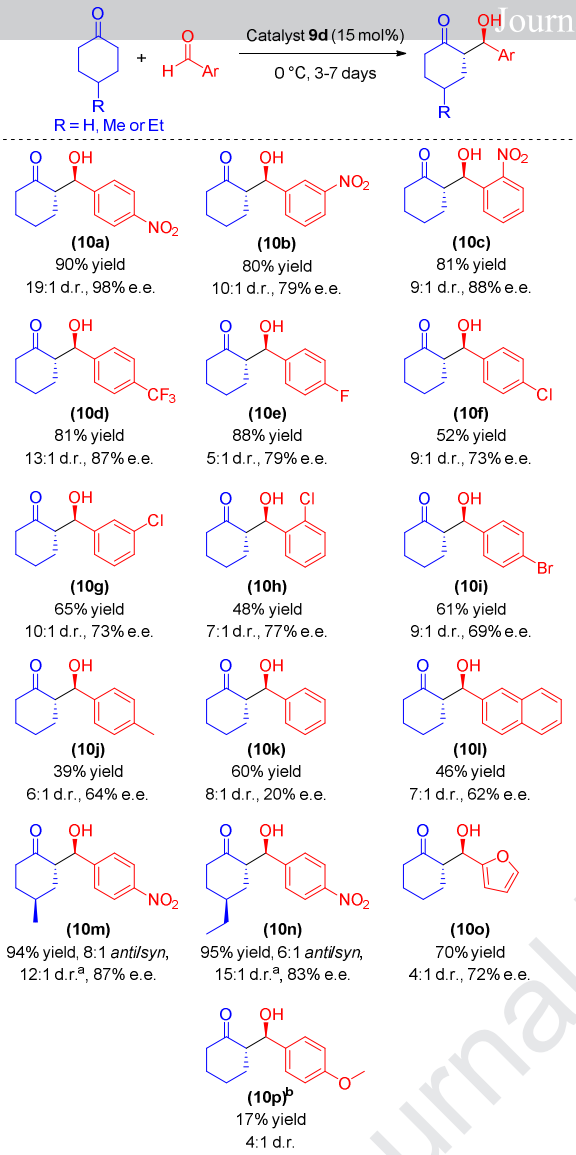
The influence of the catalyst counter-anion was also investigated. To this purpose, the substitution of trifluoroacetate moiety for trichloroacetate (catalyst **9d-TCA**) was carried out (the method for its preparation is available in the Supplementary data). After its use in the optimized reaction conditions, the aldol adduct was isolated in 80% yield, only 4:1 d.r. and 71% e.e. A control experiment employing the **salt-free 9d** catalyst was also carried out and, although the aldol product was isolated with an excellent yield (97%), the stereoselectivity drastically dropped (only 4:1 d.r. and 63% e.e.). These results suggests that the trifluoroacetate moiety is crucial for the adequate chiral induction in the desired aldol product. Interestingly, good results for catalysts bearing fluorinated counter-anions were previously reported by other groups for the asymmetric aldol reaction [21].

Next, aiming to gain further insights of the importance and extension of the polyol group interactions in the asymmetric induction process, we prepared an analogue of catalyst **9d** (hereby named **9d-*rac***) employing glycerol as starting material (full details of this preparation are available in the Supplementary data). Thus, the polyol precursor is formed as a racemic mixture and, after condensation with the *L*-proline moiety affords the catalyst as a mixture of diasteomers. The use of this novel catalyst (**9d-*rac***) in the optimized reaction conditions resulted in the desired aldol adduct in 71% yield and with a considerable drop in the reaction diastereoselectivity (only 4:1 d.r.) and enantiomeric excess (75%). This suggests that the polyol side-chain enhance reaction stereocontrol toward the major aldol isomer through selectively stabilizing the transition state leading to this isomer.

Finally, for the determination of the relative and absolute stereochemistry of the synthesized derivative, an ^{1}H NMR analysis was carried out and indicated, by comparison with literature data [25], *anti* as the major isomer. Moreover, enantiodiscriminating high-performance liquid chromatography (HPLC) analysis corroborated with these data and also revealed (S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one as the major stereoisomer.

2.3. Reaction scope

Having established the best reaction conditions and determined the absolute configuration of the product, the evaluation of the substrate scope was then carried out. Various aromatic aldehydes and substituted cyclohexanones were well tolerated under the optimized reaction conditions (Scheme 5). Aromatic aldehydes bearing electron-withdrawing groups in *para*, *meta* or even in the sterically bulky *ortho*-position were well tolerated, affording the desired compounds **10a-d** in 80-90% yield, 9:1 to 19:1 d.r. and up to 98% e.e.



[a]Diastereoisomeric ratio of the two *anti* isomers.
[b]The enantiomeric excess of this derivative was not determined.

Scheme 5. Reaction scope.

Moreover, the use of aryl groups bearing halides was also possible. For example, the use of 2-chlorobenzaldehyde resulted in the derivative **10h** in moderate yield (48%) and good stereoselectivity (7:1 d.r. and 77% e.e.). On the other hand, although aldehydes with naphthyl and toluyl groups resulted in the desired adducts (**10l** and **10j**, respectively) in moderate yields and stereoselectivities (up to 7:1 d.r and 64% e.e.), a considerable drop in the enantiomeric excess was observed when employing benzaldehyde (only 20% e.e.).

Most interestingly, the use of substituted cyclohexanones was also possible, affording the derivatives **10m** and **10n**, in which a total of eight stereoisomers are possible to occur. These compounds were obtained in excellent yields (up to 95%), with a good selectivity towards the two *anti* diastereomers (up to 8:1 d.r.), an excellent diastereomeric ratio between these two stereoisomers (between 12:1 and 15:1 d.r.) and a good enantiomeric ratio (up to 87% e.e.). Although a good yield was observed when employing a heteroaryl substituted aldehyde (compound **10o**), only a moderate stereoselectivity was detected (4:1 d.r and 72% e.e.). Moreover, the use of an electron-donating group was not well tolerated, affording the desired adduct (compound **10p**) in low yield (only 17%) and moderate diastereoselectivity (4:1 d.r.). This is probably related to the aldol carbon-carbon bond formation step, in which less electrophilic aldehyde carbonyl groups are less favored. Finally, acetone was tested as aldol donor in the presence of 4-nitrobenzaldehyde, but lead only to the aldol condensation product.

2.4. Computational details

We then turned our attention toward the understanding of the basics of this reaction by investigating a plausible key intermediate and the chiral induction process. To this purpose, theoretical calculations were then carried out. All calculations were performed using the Gaussian09 package [26]. Unless otherwise stated, calculations were performed at a pressure equal to 1 atm and temperature of 273.15 K. The structural optimizations at the gas phase of all structures, molecular complexes (MCs) and transition states (TSs) were carried out employing the M06-2X functional [27] and the 6-31G(d,p) basis set. A vibrational analysis was performed to check the identity of all stationary points and in the attainment of the thermal corrections to the Gibbs free energy. Transition states were optimized employing the Berny algorithm or the QST2 method and confirmed to have only one imaginary frequency (full details concerning the theoretical data are available in the Electronic Supplementary Information).

Next, for the attainment of the electronic energy at the desired level of theory, single-point energy calculations were subsequently carried out using the previously optimized geometries at the M06-2X-D3/6-31++G(d,p) level of theory and, since no solvent was employed during the reactions, the Solvation Model Based on Density (SMD) for cyclohexanone (reagent) was employed [28]. The Gibbs Free Energy of each structure was then calculated by equation 1 [29], in which the terms are, respectively, the Electronic Energy, the solvation Gibbs Free Energy, and the thermal correction to enthalpy and entropy.

$$G^{\circ}_{sol} = E_{Gas} + G_{Solv} + G^{\circ}_{T} \qquad (1)$$

2.5. Mechanistic investigation

Prolinamide-based organocatalysts are well known for activating substrates through iminium/enamine formation [13]. In prolinamide catalyzed aldol reactions, the stereoinduction step occurs during the addition of the previously *in situ* formed enamine to the aldehyde. It is also reported in the literature that, although the rotation over the C-N bond is possible, enamines can preferentially adopt a conformation *s-cis* or *s-trans* [30]. Due to that, both conformers were theoretically evaluated (Figure 1) and it was found that they are very close in energy (ΔG 0.52 kcal/mol). Although both conformers presented two similar hydrogen bonding interactions, its distance considerably varied. For example, the interaction between hydroxyl groups was 2.88 Å for *s-cis* conformer and 2.68 Å for *s-trans*; on the other hand, the hydrogen bonding interaction between the amide carbonyl and one of the hydroxyl groups was stronger for the *s-cis* conformer (2.03 Å against 2.15 Å of the *s-trans* enamine).

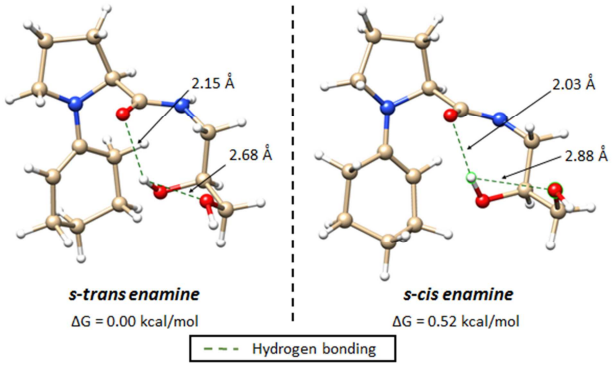


Figure 1. Enamine conformers.

Since no selectivity towards a specific conformer was observed, the C-C bond formation step involving both enamine substrates and the formation of all possible products were evaluated. To this purpose, the 4-nitrobenzaldehyde was chosen as the aldol acceptor and a total of eight different pathways were simulated. Interestingly, molecular complexes between the enamine and the aldehyde are generally thermodynamically unfavored in comparison with the isolated reagents, especially for the *s-cis* enamine (ΔG 4.76-7.68 kcal/mol). Thus, the approximation between aldehyde and *s-trans* enamine (ΔG -0.90 to 4.33 kcal/mol) is much more probable to occur.

Moreover, the results concerning the aldol product formation are summarized in Table 3 and reveal some interesting conclusions. First, among all possible transition states, six presented hydrogen bonding interactions between the aldehyde carbonyl and the enamine side-chain derived from the prolinamide group (entries 1, 2, 5, 6, 7, and 8), one presented a hydrogen bonding interaction involving the aldehyde nitro group (entry 4) and the other did not present any interaction involving the aldehyde moiety (entry 3).

Table 3. Reaction pathways towards all possible stereoisomers (kcal/mol).

Entry	Enamine	Enamine face	Aldehyde face	Final product[a]	ΔΔG‡	ΔΔG
1	***s-trans***	Re	Si	SS	5.78	2.13
2	***s-trans***	Re	Re	SR	0.00	0.00
3	***s-trans***	Si	Si	RS	8.57	22.11
4	***s-trans***	Si	Re	RR	12.41	26.05
5	***s-cis***	Re	Si	SS	11.98	7.24
6	***s- cis***	Re	Re	SR	5.36	10.64
7	***s- cis***	Si	Si	RS	10.18	3.10
8	***s- cis***	Si	Re	RR	6.69	10.17

[a]Stereochemistry related to the final product after iminium hydrolysis: first stereocenter related to the α-carbonyl carbon; second stereocenter related to the carbon bonded to the hydroxyl group.

Most interestingly, the lower energy transition state (entry 2) involved the *s-trans* enamine and, simultaneously, presented three hydrogen bonding interactions between the enamine side-chain and the aldehyde carbonyl group (Figure 2). These interactions are considerably strong (between 1.79 and 2.16 Å), lowering the transition state barrier to 23.19 kcal/mol. Noteworthy, the second most accessible transition state (entry 6) also led to the experimentally observed stereoisomer but through the *s-cis* enamine. Moreover, the molecular complex formed right after the carbon-carbon bond formation also presented lower energy for the major stereoisomer, with a ΔG of only 0.06 kcal/mol. Thus, the formation of this stereoisomer is both kinetic and thermodynamically favored along all other possible pathways and perfectly explains the experimental data.

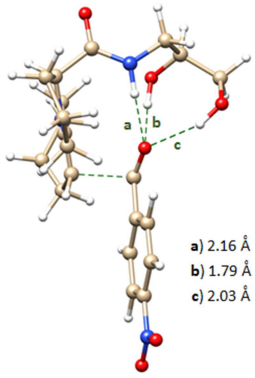


Figure 2. Transition state of the reaction between *s-trans* enamine and 4-nitrobenzaldehyde leading to (S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one.

3. Conclusion

In summary, four novel organocatalysts were synthesized by the coupling of an amino acid and a chiral amine. These catalysts were prepared along eight reaction steps and then applied in a solvent-free asymmetric aldol reaction. The best results were obtained for the prolinamide catalyst **9d**, allowing the access to the desired adducts in moderate to excellent yields, up to 19:1 d.r. and 98% e.e. Noteworthy, even sterically bulky aldehydes and substituted cyclohexanones were successfully employed in the optimized reaction conditions. The relative and absolute configuration of the products was confirmed through ^{1}H NMR and enantiodiscriminating HPLC. Control experiments revealed that the trifluoroacetate counter-anion is crucial for the attainment of higher stereoselectivities. Finally, theoretical calculations were performed to gain insights towards the chiral induction mechanism and suggested that several hydrogen bonding interactions between the enamine intermediate and the aldehyde are responsible for further stabilization of the transition state that leads to the observed stereoisomer.

4. Experimental section

4.1. General remarks

All purchased solvents and chemicals were employed without further purification. The reactions were monitored by thin-layer chromatography performed on TLC plates (silica gel 60 F254) and visualized by a UV lamp; column chromatography was carried out employing 230−400 mesh silica gel. Reported yields refer to chromatographically purified and spectroscopically pure compounds. Chemical shifts for ^{1}H NMR were reported as δ (parts per million) relative to chloroform signal of at 7.26 ppm (singlet – solvent $CDCl_3$) or to the water signal at 4.79 ppm (broad - solvent deuterium oxide). Chemical shifts for ^{13}C {^{1}H} NMR were reported as δ relative to the central line signal of the $CDCl_3$ triplet at 77.2 ppm or to methanol (internal standard) at 49.5 ppm. The ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C {^{1}H} NMR spectra were recorded at 125 MHz. Chemical shifts are reported employing the following peak abbreviations: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; dq, doublet of

quartet; t, triplet; tdd, triplet of doublet of doublet; q, quartet; oct, octet; m, multiplet. Melting points were acquired on a melting point apparatus and optical rotations on a polarimeter. Enantiodiscriminating HPLC was performed using a 4.6 × 25 cm^2 Chiralpak IB column (isocratic elution using hexane/isopropanol 90:10 or 85:5; flow 0.5 or 0.9 mL/min). The elemental composition of the catalysts was determined using a Perkin Elmer 2400 CHNS/O Series II microanalyzer.

*4.2. General Procedure for the synthesis of product **2***

In a round-bottom flask, 10.0 g of *D*-mannitol (54.9 mmol) was added, followed by addition of 30 mL of dimethylsulfoxide (DMSO). The reaction mixture was kept under magnetic stirring at 0 °C for 30 minutes. Next, 0.2 g of *p*-toluenesulfonic acid (2 mol%) and 20 mL of acetone were added and the reaction kept at 0 °C for 30 minutes and room temperature for 15 hours. Next, the crude reaction mixture was diluted in ethyl acetate (30.0 mL) and a liquid-liquid extraction employing a 5% m/v of an aqueous solution of $NaHCO_3$ (three aliquots of 100.0 mL) carried out. The organic phase was then dried under reduced pressure and further purification by column chromatography (silica gel) employing isocratic eluent 1:1 ethyl acetate/hexane was carried out.

(1S,2S)-1,2-bis((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**2**): White solid, 11.1 g, yield: 77%. m.p.: 118.0-120.0 °C. $[\alpha]_D^{25}$ +2.4 (c 1.0, EtOH). IR (ATR) ν (cm^{-1}): 3389, 2978, 2942, 2887, 2849, 1628, 1445, 1402, 1366, 1162, 1076, 1003, 918. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.17 (*q*, *J* 6.3 Hz, 2H), 4.11 (*dd*, *J* 8.6 Hz, *J* 6.4 Hz, 2H), 3.97 (*dd*, *J* 8.6 Hz, *J* 5.6 Hz, 2H), 3.74 (*t*, *J* 6.6 Hz, 2H), 2.69 (*d*, *J* 6.5 Hz, 2H), 1.41 (*s*, 6H), 1.35 (*s*, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 109.5, 76.4, 71.3, 66.9, 26.9, 25.3.

*4.3. General Procedure for the synthesis of product **3***

In a round-bottom flask, 11.0 g of compound **2** (42.1 mmol) was added, followed by addition of 100 mL of an aqueous solution of $NaHCO_3$ (5 % m/v). The reaction mixture was kept under magnetic stirring at 0 °C for 10 minutes. Next, 100 mL of an aqueous solution containing 18.0 g (84.2 mmol, 2 equiv.) of sodium periodate was slowly added to the reaction mixture. The reaction was kept under magnetic stirring for 1 hour, after which 100 mL of ethanol was added. The crude reaction mixture was then filtered off to remove the unreacted periodate. The remaining solution was then cooled to 0 °C and 3.2 g (84.2 mmol, 2 equiv.) of sodium borohydride was then added. The reaction mixture was then kept under magnetic stirring for 2 hours and then filtered off. The solid was diluted in chloroform and submitted to a liquid-liquid extraction employing distilled water. Finally, the organic phase was dried and the compound **3** distilled under reduced pressure (5 mmHg).

(S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**3**): Colorless oil, 7.0 g, yield: 63%. $[\alpha]_D^{20}$ + 14.7° (pure). IR (ATR) ν (cm^{-1}): 3414, 2990, 2934, 2887, 1641, 1377, 1261, 1211, 1150, 1046. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.23 (*tdd*, *J* 6.5 Hz, *J* 5.2 Hz, *J* 3.8 Hz, 1H), 4.03 (*dd*, *J* 8.2 Hz, *J* 6.6 Hz, 1H), 3.78 (*dd*, *J* 8.2 Hz, *J* 6.5 Hz, 1H), 3.72 (*dd*, *J* 11.6 Hz, *J* 3.6 Hz, 1H), 3.58 (*dd*, *J* 11.6 Hz, *J* 5.1 Hz, 1H), 2.10 (*br*, 1H), 1.43 (*s*, 3H), 1.36 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 109.5, 76.3, 65.8, 63.1, 26.8, 25.4.

*4.4. General Procedure for the synthesis of product **4***

In a round-bottom flask, 3.0 g of product **3** (22.7 mmol) was added, followed by addition of 100 mL of toluene. Next, 7.2 g of triphenylphosphine (27.3 mmol, 1.2 equiv.), 2.3 g (34.1 mmol, 1.5 equiv.) of imidazole and 7.5 g of I_2 (29.6 mmol, 1.3 equiv.) were added. The reaction mixture was kept under reflux at 90 °C for 2 hours. Next, the solvent was dried under reduced pressure and the crude reaction mixture diluted in chloroform. A liquid-liquid extraction employing a saturated aqueous solution of $Na_2S_2O_3$ (two aliquots of 100.0 mL) was then carried out. The organic phase was then dried under reduced pressure and further purification by column chromatography (silica gel) employing isocratic eluent 2:8 ethyl acetate/hexane was carried out.

(R)-4-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (**4**): Colorless oil, 4.0 g, yield: 73%. $[\alpha]_D^{20}$ + 33.3° (c 1.8, ethanol). IR (ATR) ν (cm^{-1}): 2984, 2929, 2873, 1371, 1211, 1144, 1040. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.30-4.25 (*m*, 1H), 4.14 (*dd*, *J* 8.6 Hz, *J* 6.1 Hz, 1H), 3.78 (*dd*, *J* 8.6 Hz, *J* 5.5 Hz, 1H), 3.25 (*dd*, *J* 9.8 Hz, *J* 4.6 Hz, 1H), 3.14 (*dd*, *J* 9.8 Hz, *J* 8.5 Hz, 1H), 1.45 (*s*, 3H), 1.34 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 110.7, 75.8, 69.8, 27.3, 25.7, 6.8.

*4.5. General Procedure for the synthesis of product **5***

In a round-bottom flask, 3.0 g of product **4** (12.4 mmol) was added, followed by the addition of 20 mL of dimethylformamide. Next, 1.1 g of sodium azide (16.1 mmol, 1.3 equiv.) was added. The reaction mixture was kept under reflux at 60 °C for 6 hours. The crude reaction mixture was then diluted in hexane (100 mL) and washed twice with a saturated aqueous solution of NaCl (2x60 mL). The organic phase was then dried under reduced pressure and further purification by column chromatography (silica gel) employing isocratic eluent 1:9 ethyl acetate/hexane was carried out.

(S)-4-(azidomethyl)-2,2-dimethyl-1,3-dioxolane (**5**): Colorless oil, 1.4 g, yield: 73%. $[\alpha]_D^{20}$ - 47.1° (c 2.8, $CHCl_3$). IR (ATR) ν (cm^{-1}): 2984, 2929, 2873, 1371, 1211, 1144, 1040. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.32-4.21 (*m*, 1H), 4.06 (*dd*, *J* 8.5 Hz, *J* 6.4 Hz, 1H), 3.77 (*dd*, *J* 8.4 Hz, *J* 5.9 Hz, 1H), 3.40 (*dd*, *J* 12.8 Hz, *J* 4.7 Hz, 1H), 3.30 (*dd*, *J* 12.8 Hz, *J* 5.6 Hz, 1H), 1.47 (*s*, 3H), 1.36 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 110.1, 74.7, 66.8, 53.0, 26.8, 25.4.

*4.6. General Procedure for the synthesis of product **6***

In a round-bottom flask, 1.0 g of product **5** (6.4 mmol) was added, followed by the addition of 15 mL of methanol. Next, 0.11 g (0.96 mmol, 15 mol%) of Pd/C was added. The atmosphere was then replaced by hydrogen. The reaction mixture was kept at room temperature for 24 hours with a balloon of H_2. The reaction mixture was then filtered off to remove the Pd/C and the solvent removed under reduced pressure. The crude reaction mixture was then diluted in dichloromethane (50 mL) and washed twice with a saturated aqueous solution of NaCl (2x30 mL). The organic phase was then dried under reduced pressure.

(S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (**6**): Yellow oil, 680 mg, yield: 81%. $[\alpha]_D^{20}$ - 24.0° (c 1.0, ethanol). IR (ATR) ν (cm^{-1}): 3365, 2984, 2929, 1653, 1598, 1457, 1371, 1248, 1211, 1051. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.13-4.06 (*m*, 1H), 4.02-3.99 (*m*, 1H), 3.65-3.62 (*m*, 1H), 2.81 (*dd*, *J* 13.1 Hz, *J* 4.2 Hz, 1H), 2.75 (*dd*, *J* 13.1 Hz, *J* 6.3 Hz, 1H), 1.61 (s, 2H), 1.39 (*s*, 3H), 1.33 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 109.3, 77.4, 67.0, 44.8, 27.0, 25.4.

*4.7. General Procedure for the synthesis of products **7a-d***

Boc-protected amino acids were prepared following a literature method [17]. Initially, to a solution of water/1,4-dioxane (3:2 v/v), 5.0 mmol of an amino acid (*L*-valine, *L*-

leucine, *L*-phenylalanine or *L*-proline) and 0.3 g of $NaHCO_3$ were added. Next, 7.5 mmol of Boc anhydride (1.5 equiv.) were added to this mixture. The reaction mixture was stirred at room temperature for 24 hours. The crude reaction mixture was then diluted in water (50.0 mL) and a liquid-liquid extraction employing 40 mL of ethyl acetate was carried out to remove the residual Boc_2O. The pH of the water phase was then adjusted to 1 with an aqueous solution of HCl (2M). Next, a liquid-liquid extraction employing ethyl acetate was carried out (three aliquots of 100.0 mL). The organic phase was then dried under reduced pressure and further purification by column chromatography (silica gel) employing isocratic eluent 9:1 dichloromethane/methanol was carried out.

(Tert-butoxycarbonyl)-L-valine (**7a**): Colorless oil, 890 mg, yield: 82%. $[\alpha]_D^{25}$ -10.0° (c 1.0, DMF). IR (ATR) ν (cm^{-1}): 3536, 3325, 2968, 2934, 1718, 1505, 1394, 1368, 1160. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.45 (*br*, 1H), 5.04 (*d*, *J* 8.5 Hz, 1H), 4.25 (*dd*, *J* 9.0 Hz, *J* 4.7 Hz, 1H), 2.21-2.18 (*m*, 1H), 1.44 (*s*, 9H), 0.99 (*d*, *J* 6.8 Hz, 3H), 0.92 (*d*, *J* 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 177.2, 156.0, 80.2, 58.6, 31.2, 28.4, 19.04, 17.6.

(Tert-butoxycarbonyl)-L-leucine (**7b**): White solid, 1132 mg, yield: 98%. $[\alpha]_D^{25}$ -29.5° (c 1.0, DMF). m.p.: 67.0-70.0 °C. IR (ATR) ν (cm^{-1}): 3448, 3320, 2961, 2876, 1714, 1510, 14. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.71 (*br*, 1H), 4.90 (*d*, *J* 8.1 Hz, 1H), 4.31 (*q*, *J* 6.9 Hz, 1H), 1.77-1.72 (*m*, 1H), 1.70-1.64 (*m*, 1H), 1.57-1.48 (*m*, 1H), 1.44 (*s*, 9H), 0.95 (*d*, *J* 6.6 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 178.1, 155.8, 80.4, 52.1, 41.6, 28.4, 24.9, 23.0, 21.9.

(Tert-butoxycarbonyl)-L-phenylalanine (**7c**): White solid, 1113 mg, yield: 84%. $[\alpha]_D^{25}$ -20.2° (c 1.0, DMF). m.p.: 62.0-65.0 °C. IR (ATR) ν (cm^{-1}): 3436, 2986, 2929, 1712, 1505, 1370, 1258, 1160. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (*t*, *J* 7.2 Hz, 2H), 7.26 (*t*, *J* 7.3 Hz, 1H), 7.18 (*d*, *J* 7.4 Hz, 2H), 4.96 (*d*, *J* 7.4 Hz, 1H), 4.61 (*q*, *J* 7.4 Hz, 1H), 3.20 (*dd*, *J* 13.9 Hz, *J* 5.1 Hz, 1H), 3.08 (*dd*, *J* 13.9 Hz, *J* 6.5 Hz, 1H), 1.42-1.30 (*s*, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 176.4, 155.5, 136.0, 129.5, 128.8, 127.3, 80.5, 54.4, 37.9, 28.4.

(Tert-butoxycarbonyl)-L-proline (**7d**): White solid, 914 mg, yield: 85%. $[\alpha]_D^{25}$ -46.0° (c 1.0, DMF). m.p.: 135.0-137.0 °C. IR (ATR) ν (cm^{-1}): 3498, 3125, 2976, 2884, 1747, 1697, 1418, 1368, 1166, 1125. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 6.61 (*br*, 1H), 4.35-4.24 (*m*, 1H), 3.55-3.33 (*m*, 2H), 2.30-2.28 (*m*, 1H), 2.09-2.04 (*m*, 1H), 1.95-1.90 (*m*, 2H), 1.48-1.42 (*m*, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ: 178.7, 174.8, 156.8, 154.0, 81.7, 80.5, 59.3, 59.0, 47.2, 46.5, 31.0, 28.5, 28.4, 24.5, 23.8.

*4.8. General Procedure for the synthesis of products **8a-d***

In a round-bottom flask, 100 mg of product **6** (0.75 mmol) and 0.75 mmol of the Boc protected amino acid **7a-d** (1.0 equiv.) were added, followed by the addition of 8 mL of dichloromethane. Next, 155 mg of *N*,*N*'-dicyclohexylcarbodiimide (0.1 mmol, 1.3 equiv.) and 9 mg of 4-dimethylaminopyridine (0.08 mmol, 10 mol%) were added. The reaction mixture was kept under magnetic stirring at room temperature for 24 hours. The reaction mixture was then filtered off for to remove the *N*,*N*'-dicyclohexylurea and the solvent was removed under reduced pressure. Further purification by column chromatography (silica gel) employing isocratic eluent 1:1 ethyl acetate/hexane was carried out.

Tert-butyl ((S)-1-((((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**8a**): White solid, 201 mg, yield: 81%. $[\alpha]_D^{23}$ -16.0° (c 1.0, $CHCl_3$). m.p.: 101.0-103.0 °C. IR (ATR) ν (cm^{-1}): 3340, 3309, 2978, 2930, 2868, 1683, 1653, 1518, 1365, 1211, 1169. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.26 (*br*, 1H), 5.01 (*br*, 1H), 4.21 (*qd*, *J* 6.3 Hz, *J* 3.7 Hz, 1H), 4.02 (*dd*, *J* 8.4 Hz, *J* 6.5 Hz, 1H), 3.94-3.88 (*m*, 1H), 3.61 (*dd*, *J* 8.4 Hz, *J* 6.4 Hz, 1H), 3.55 (*ddd*, *J* 13.9 Hz, *J* 6.0 Hz, *J* 3.7 Hz, 1H), 3.32 (*dt*, *J* 14.0 Hz, *J* 5.9 Hz, 1H), 2.17 (*br*, 1H), 1.44 (*s*, 9H), 1.43 (*s*, 3H), 1.33 (*s*, 3H), 0.96 (*d*, *J* 6.8 Hz, 3H), 0.91 (*d*, *J* 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 172.0, 156.0, 109.6, 80.1, 74.6, 66.8, 60.3, 41.5, 30.7, 28.4, 26.9, 25.3, 19.4, 17.8. *Anal.* calcd. For $C_{16}H_{30}N_2O_5$: C 58.16, H 9.15, N 8.48; found: C 58.43, H 8.67, N 8.52.

Tert-butyl ((S)-1-((((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**8b**): White solid, 183 mg, yield: 71%. $[\alpha]_D^{23}$ -20.0 (c 1.0, $CHCl_3$). m.p.: 96.0-98.0 °C. IR (ATR) ν (cm^{-1}): 3376, 3328, 2965, 2929, 2873, 1702, 1647, 1501, 1371, 1162. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.48 (*br*, 1H), 4.91 (*d*, *J* 7.3 Hz, 1H), 4.19 (*qd*, *J* 6.3 Hz, *J* 3.9 Hz, 1H), 4.14-4.05 (*m*, 1H), 4.00 (*dd*, *J* 8.3 Hz, *J* 6.5 Hz, 1H), 3.60 (*dd*, *J* 8.4 Hz, *J* 6.5 Hz, 1H), 3.52-3.49 (*m*, 1H), 3.31-3.27 (*m*, 1H), 1.69-1.63 (*m*, 2H), 1.50-1.46 (*m*, 1H), 1.42 (*s*, 12H), 1.32 (*s*, 3H), 0.93 (*d*, *J* 6.4 Hz, 3H), 0.91 (*d*, *J* 6.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 173.1, 155.8, 109.5, 80.2, 74.6, 66.8, 53.3, 41.5, 41.4, 28.4, 26.9, 25.4, 24.9, 23.1, 22.1. *Anal.* calcd. For $C_{17}H_{32}N_2O_5$: C 59.28, H 9.36, N 8.13; found: C 60.27, H 8.67, N 8.34.

Tert-butyl ((S)-1-((((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**8c**): White solid, 185 mg, yield: 65%. $[\alpha]_D^{23}$ -2.0° (c 1.0, $CHCl_3$). m.p.: 104.0-106.0 °C. IR (ATR) ν (cm^{-1}): 3340, 3315, 2984, 2929, 2868, 1683, 1659, 1512, 1371, 1205, 1162. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (*t*, *J* 7.3 Hz, 2H), 7.25-7.23 (*m*, 1H), 7.22-7.19 (*m*, 2H), 6.08 (*br*, 1H), 5.02 (*br*, 1H), 4.33 (*br*, 1H), 4.05 (*br*, 1H), 3.97-3.94 (*m*, 1H), 3.52 (*dd*, *J* 8.3 Hz, *J* 6.5 Hz, 1H), 3.43-3.42 (*m*, 1H), 3.27-3.22 (*m*, 1H), 3.06-3.05 (*m*, 2H), 1.40 (*s*, 9H), 1.35 (*s*, 3H), 1.30 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 171.6, 155.5, 136.8, 129.4, 128.9, 127.2, 109.5, 80.4, 74.4, 66.8, 56.1, 41.6, 38.7, 28.4, 26.8, 25.3. *Anal.* calcd. For $C_{20}H_{30}N_2O_5$: C 63.47, H 7.99, N 7.40; found: C 63.85, H 7.70, N 7.36.

Tert-butyl (S)-2-(2-((((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate (**8d**): White solid, 145 mg, yield: 59%. $[\alpha]_D^{23}$ -80° (c 1.0, $CHCl_3$). m.p.: 155.0-156.0 °C. IR (ATR) ν (cm^{-1}): 3340; 2984; 2929; 2865; 1683; 1647; 1531; 1390; 1365; 1156; 1125. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 6.95 (*br*, 0.5H), 6.44 (*br*, 0.5H), 4.24-4.19 (*m*, 2H), 4.02 (*br*, 1H), 3.60-3.57 (*m*, 1H), 3.45 (*br*, 4H), 2.30-2.14 (*m*, 2H), 1.87 (*br*, 2H), 1.45 (*s*, 9H), 1.42 (*s*, 3H), 1.32 (*s*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ: 173.1, 172.6, 155.8, 154.9, 109.4, 80.7, 74.6, 66.7, 61.5, 60.4, 47.2, 41.5, 31.2, 28.4, 26.8, 25.1, 24.6, 23.8. *Anal.* calcd. For $C_{16}H_{28}N_2O_5$: C 58.52, H 8.59, N 8.53; found: C 58.57, H 8.31, N 8.56.

*4.9. General Procedure for the synthesis of products **9a-d***

In a round-bottom flask, 0.3 mmol of product **8a-d**, 1.5 mL of dichloromethane and 6.6 mmol of trifluoroacetic acid (22 equiv.) were added. The reaction mixture was kept under magnetic stirring at room temperature for 3 h. Next, the solvent was removed under reduced pressure.

(S)-1-(((S)-2,3-dihydroxypropyl)amino)-3-methyl-1-oxobutan-2-aminium 2,2,2-trifluoroacetate (**9a**): Yellow oil, 81 mg, yield: 89%. $[\alpha]_D^{23}$ +73.0° (c 0.3, CH_3OH). IR (ATR) ν (cm^{-1}): 3351, 2965, 2923, 2849, 1659, 1438, 1187, 1131. ^1H NMR (500 MHz, D_2O) δ: 3.80-3.76 (*m*, 1H), 3.73 (*d*. *J* 6.1 Hz, 1H), 3.56 (*dd*, *J* 11.8 Hz, *J* 4.3 Hz, 1H), 3.48 (*dd*, *J* 11.8 Hz, *J* 6.2 Hz, 1H), 3.40 (*dd*, *J* 14.0 Hz, *J* 4.4 Hz, 1H), 3.23 (*dd*, *J* 14.1 Hz, *J* 7.6 Hz, 1H), 2.16 (*oct*, *J* 6.8 Hz, 1H), 0.98 (*d*, *J* 6.8 Hz, 3H), 0.97 (*d*, *J* 6.9 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, D_2O) δ: 170.5, 163.5 (*q*, *J* 34 Hz), 116.9 (*q*, *J* 290 Hz), 70.7, 63.9, 59.3, 42.4, 30.5, 18.2, 17.4. *Anal*. calcd. For $C_{10}H_{18}F_3N_2O_4$: C 39.48, H 6.29, N 9.21; found: C 38.72, H 5.97, N 8.03.

(S)-1-(((S)-2,3-dihydroxypropyl)amino)-4-methyl-1-oxopentan-2-aminium 2,2,2-trifluoroacetate (**9b**): Yellow oil, 86 mg, yield: 90%. $[\alpha]_D^{23}$ +18.0° (c 1.0, CH_3OH). IR (ATR) ν (cm^{-1}): 3221, 2929, 2855, 1659, 1413, 1193, 1139. ^1H NMR (500 MHz, D_2O) δ: 3.94-3.92 (*m*, 1H), 3.83-3.81 (*m*, 1H), 3.61 (*dd*, *J* 11.7 Hz, *J* 4.2 Hz, 1H), 3.53 (*dd*, *J* 11.7 Hz, *J* 6.2 Hz, 1H), 3.44 (*dd*, *J* 14.0 Hz, *J* 4.5 Hz, 1H), 3.29 (*dd*, *J* 14.1 Hz, *J* 7.5 Hz, 1H), 1.71-1.70 (*m*, 2H), 1.46-1.36 (*m*, 1H), 0.97-0.95 (*m*, 6H). ^{13}C {^1H} NMR (125 MHz, D_2O) δ: 172.7, 163.6 (*q*, *J* 35 Hz), 117.0 (*q*, *J* 291 Hz), 70.7, 63.9, 52.4, 42.6, 40.9, 24.6, 22.4, 21.5. *Anal*. calcd. For $C_{11}H_{20}F_3N_2O_4$: C 41.51, H 6.65, N 8.80; found: C 40.72, H 6.54, N 8.09.

(S)-1-(((S)-2,3-dihydroxypropyl)amino)-1-oxo-3-phenylpropan-2-aminium 2,2,2-trifluoroacetate (**9c**): Yellow oil, 97 mg, yield: 92%. $[\alpha]_D^{23}$ +37.5° (c 0.8, CH_3OH). IR (ATR) ν (cm^{-1}): 3340, 2959, 2929, 2855, 1666, 1438, 1192, 1131. ^1H NMR (500 MHz, D_2O) δ: 7.44-7.35 (*m*, 3H), 7.28 (*d*, *J* 7.6 Hz, 2H), 4.19 (*t*, *J* 7.3 Hz, 1H), 3.57-3.65 (*m*, 1H), 3.46 (*dd*, *J* 11.8 Hz, *J* 4.1 Hz, 1H), 3.39 (*dd*, *J* 11.8 Hz, *J* 6.3 Hz, 1H), 3.29 (*dd*, *J* 14.0 Hz, *J* 4.5 Hz, 1H), 3.22-3.13 (*m*, 3H). ^{13}C {^1H} NMR (125 MHz, D_2O) δ: 171.5, 163.6 (*q*, *J* 36 Hz), 134.9, 129.9, 129.7, 128.5, 116.9 (*q*, *J* 289 Hz), 70.6, 63.8, 54.9, 42.5, 38.0. *Anal*. calcd. For $C_{14}H_{18}F_3N_2O_4$: C 47.73, H 5.44, N 7.95; found: C 48.73, H 5.91, N 6.83.

(S)-2-(2-(((S)-2,3-dihydroxypropyl)amino)-2-oxoethyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (**9d**): Yellow oil, 79 mg, yield: 87%. $[\alpha]_D^{23}$ -30.0° (c 1.0, CH_3OH). IR (ATR) ν (cm^{-1}): 3359, 3266, 2959, 2923, 2855, 1666, 1567, 1426, 1187, 1125. ^1H NMR (500 MHz, D_2O) (mixture of rotamers) δ: 4.38 (*t*, *J* 7.3 Hz, 1H), 3.82 (*ddd*, *J* 11.1 Hz, *J* 6.8 Hz, *J* 4.6 Hz, 1H), 3.61 (*dd*, *J* 11.8 Hz, *J* 4.3 Hz, 1H), 3.53 (*dd*, *J* 11.8 Hz, *J* 6.3 Hz, 1H), 3.49-3.36 (*m*, 3H), 3.30 (*dd*, *J* 14.0 Hz, *J* 7.4 Hz, 1H), 2.49-2.43 (*m*, 1H), 2.09-2.06 (*m*, 3H). ^{13}C {^1H} NMR (125 MHz, D_2O) (mixture of rotamers) δ: 170.3, 162.8 (*q*, *J* 36 Hz), 116.6 (*q*, *J* 290 Hz), 70.7, 63.8, 60.4, 47.1, 42.6, 30.3, 24.4. *Anal*. calcd. For $C_{10}H_{16}F_3N_2O_4$: C 39.74, H 5.67, N 9.27; found: C 40.00, H 4.98, N 8.08.

*4.10. General Procedure for the synthesis of products **10a-p***

In a 2 mL vial, 0.75 mmol of cyclohexanone (5 equiv.) was added, followed by 0.02 mmol of catalysts **9a-d** (15 mol%) and 0.15 mmol of aldehyde. The reaction mixture was kept at 0 °C for 3-7 days. Next, the crude reaction mixture was then diluted in water (10.0 mL) and a liquid-liquid extraction employing 10 mL of dichloromethane (2x10 mL). The organic phase was dried under reduced pressure and further purification by column chromatography (silica gel) employing hexane to 3:1 hexane/ethyl acetate was carried out.

2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**10a**): Reaction time: 3 days. White solid, 34 mg, yield: 90%, 19:1 d.r., 98% e.e. IR (ATR) ν (cm^{-1}): 3505, 2923, 2849, 1683, 1598, 1506, 1341, 1291. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 2:3*) δ: 8.20-8.19 (*m*, 2H), 7.51-7,47 (*m*, 2H), 5.48 (*s*, 0.4H, *syn*), 4.89 (*d*, *J* = 8.0 Hz, 0.6H, *anti*), 4.08 (*d*, *J* = 2.2 Hz, 0.6H, *anti*), 3.19 (*d*, *J* = 2.2 Hz, 0.4H, *syn*), 2.65-2.56 (*m*, 1H), 2.51-2.46 (*m*, 1H), 2.42-2.33 (*m*, 1H), 2.13-2.08 (*m*, 1H), 1.87-1.81 (*m*, 1H), 1.72-1.51 (*m*, 4H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ: 214.9, 214.2, 149.2, 148.5, 147.7, 147.2, 128.0, 126.7, 123.7, 123.6, 74.1, 70.2, 57.3, 56.9, 42.8, 42.7, 30.9, 28.0, 27.8, 26.0, 24.9, 24.8.

2-(hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (**10b**): Reaction time: 3 days. White solid, 30 mg, yield: 80%, 10:1 d.r., 79% e.e. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:9*) δ: 8.21-8.18 (*m*, 1H), 8.17-8.11 (*m*, 1H), 7.68-7.66 (*m*, 1H), 7.54-7.50 (*m*, 1H), 5.48 (*s*, 0.1H, *syn*), 4.89 (*d*, *J* = 8.5 Hz, 0.9H, *anti*), 4.11 (*s*, 0.9H, *anti*), 3.17 (*s*, 0.1H, *syn*), 2.67-2.59 (*m*, 1H), 2.52-2.47 (*m*, 1H), 2.44-2.34 (*m*, 1H), 2.14-2.09 (*m*, 1H), 1.85-1.81 (*m*, 1H), 1.76-1.51 (*m*, 3H), 1.44-1.35 (*m*, 1H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ: 215.0, 214.3, 148.4, 143.9, 143.4, 133.3, 132.1 129.4, 129.3, 123.0, 122.2, 121.0, 74.2, 70.6, 57.3, 56.9, 42.8, 42.7, 30.9, 28.0, 27.8, 26.0, 24.9, 24.8.

2-(hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (**10c**): Reaction time: 3 days. White solid, 30 mg, yield: 81%, 9:1 d.r., 88% e.e. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:9*) δ: 8.01-7.83 (*m*, 1H), 7.77-7.76 (*m*, 1H), 7.66-7.62 (*m*, 1H), 7.44-7.41 (*m*, 1H), 5.96 (*d*, *J* = 1.6 Hz, 0.1H, *syn*), 5.44 (*d*, *J* = 7.1 Hz, 0.9H, *anti*), 2.89-2.73 (*m*, 1H), 2.46-2.41 (*m*, 1H), 2.37-2.30 (*m*, 1H), 2.12-2.07 (*m*, 1H), 1.86-1.83 (*m*, 1H), 1.80-1.73 (*m*, 1H), 1.71-1.55 (*m*, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ: 215.1, 214.2, 148.9, 147.3, 137.1, 136.8, 133.3 133.2, 129.8, 129.1, 128.5, 128.1, 124.8, 124.2, 69.9, 66.8, 57.4, 55.0, 43.0, 42.7, 31.3, 28.1, 27.9, 26.6, 25.1, 25.0.

2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (**10d**): Reaction time: 3 days. White solid, 33 mg, yield: 81%, 13:1 d.r., 87% e.e. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:9*) δ: 7.61-7.59 (*m*, 2H), 7.45-7.42 (*m*, 2H), 5.44 (*s*, 0.1H, *syn*), 4.84 (*dd*, *J* = 8.6 Hz, *J* = 2.8 Hz, 0.9H, *anti*), 4.03 (*d*, *J* = 3.0 Hz, 0.9H, *anti*), 3.11 (*d*, *J* = 3.3 Hz, 0.1H, *syn*), 2.62-2.56 (*m*, 1H), 2.51-2.45 (*m*, 1H), 2.42-2.32 (*m*, 1H), 2.13-2.08 (*m*, 1H), 1.83-1.80 (*m*, 1H), 1.74-1.62 (*m*, 1H), 1.59-1.50 (*m*, 2H), 1.39-1.29 (*m*, 1H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ: 215.3, 214.6, 145.7, 145.1, 130.2 (*q*, *J* = 32.1 Hz), 127.5, 126.2, 125.4 (*q*, *J* = 3.8 Hz), 125.3, 124.2 (*q*, *J* = 270.4 Hz), 74.4, 70.4, 57.4, 57.1, 42.8, 30.9, 28.0, 27.8, 26.0, 25.0, 24.9.

2-((4-fluorophenyl)(hydroxy)methyl)cyclohexan-1-one (**10e**): Reaction time: 5 days. White solid, 29 mg, yield: 88%, 5:1 d.r., 79% e.e. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 3:7*) δ: 7.30-7.25 (*m*, 2H), 7.05-7.00 (*m*, 2H), 5.36 (*s*, 0.3H, *syn*), 4.77 (*dd*, *J* = 8.8 Hz, 0.7H, *anti*), 3.99 (*s*, 0.7H, *anti*), 3.05 (*s*, 0.3H, *syn*), 2.59-2.54 (*m*, 1H), 2.51-2.44 (*m*, 1H), 2.40-2.32 (*m*, 1H), 2.12-2.07 (*m*, 1H), 1.87-1.79 (*m*, 1H), 1.74-1.54 (*m*, 4H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ: 215.6, 214.9, 162,5 (*d*, *J* = 244.4 Hz), 162,0 (*d*, *J* = 243.1 Hz), 137,3 (*d*, *J* = 3.0 Hz), 136,9 (*d*, *J* = 3.1 Hz), 128,8 (*d*, *J* = 8.0 Hz), 127.5 (*d*, *J* = 7.94 Hz), 115,4 (*d*, *J* = 21.3 Hz), 115,1 (*d*, *J* = 21.2 Hz), 145.1, 130.2 (*q*, *J* = 32.1 Hz), 127.5, 126.2, 125.4 (*q*, *J* = 3.8 Hz), 125.3, 124.2 (*q*, *J* = 270.4 Hz), 74.3, 70.3, 57.6, 57.3, 42.8, 30.9, 29.8, 28.1, 27.9, 26.2, 25.0, 24.9.

2-((4-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (**10f**): Reaction time: 5 days. White solid, 19 mg, yield: 52%, 9:1 d.r., 73% e.e. ^1H NMR (500 MHz, $CDCl_3$) (*syn/anti 2:3*) δ: 7.33-7.28 (*m*, 2H), 7.27-7.23 (*m*, 2H), 5.35 (*s*, 0.4H, *syn*), 4.76 (*d*, *J* = 8.7 Hz, 0.6H, *anti*), 3.98 (*d*, *J* = 2.4 Hz, 0.6H, *anti*), 3.05 (*d*, *J* = 2.6

Hz, 0.4H, *syn*), 2.58-2.53 (*m*, 1H), 2.50-2.43 (*m*, 1H), 2.40-2.32 (*m*, 1H), 2.12-2.07 (*m*, 1H), 1.87-1.78 (*m*, 1H), 1.72-1.50 (*m*, 3H), 1.33-1.27 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.5, 214.8, 140.1, 139.6, 133.7, 132.8, 128.7, 128.5, 128.4, 127.3, 74.3, 70.3, 57.5, 57.2, 42.8, 30.9, 28.1, 27.9, 26.1, 25.0, 24.9.

2-((3-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (**10g**): Reaction time: 5 days. White solid, 23 mg, yield: 65%, 10:1 d.r., 73% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:9*) δ: 7.34-7.32 (*m*, 1H), 7.29-7.25 (*m*, 2H), 7.24-7.16 (*m*, 1H), 5.36 (*s*, 0.1H, *syn*), 4.76 (*dd*, *J* = 8.7 Hz, *J* = 2.7 Hz, 0.9H, *anti*), 3.99 (*d*, *J* = 2.8 Hz, 0.9H, *anti*), 3.05 (*d*, *J* = 3.2 Hz, 0.1H, *syn*), 2.60-2.55 (*m*, 1H), 2.51-2.44 (*m*, 1H), 2.41-2.32 (*m*, 1H), 2.13-2.07 (*m*, 1H), 1.88-1.79 (*m*, 1H), 1.73-1.52 (*m*, 3H), 1.36-1.26 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.4, 214.7, 143.8, 143.2, 134.5, 134.4, 129.8, 129.6, 128.2, 127.3, 126.2, 125.4, 124.0, 74.4, 70.2, 57.4, 57.1, 42.9, 42.8, 30.9, 28.1, 27.9, 26.1, 25.0, 24.9.

2-((2-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (**10h**): Reaction time: 5 days. White solid, 17 mg, yield: 48%, 7:1 d.r., 77% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*anti*) δ: 7.56-7.54 (*m*, 1H), 7.34-7.29 (*m*, 2H), 7.23-7.19 (*m*, 1H), 5.35 (*dd*, *J* = 8.1 Hz, *J* = 6.6 Hz, 1H), 4.02 (*d*, *J* = 3.9 Hz, 1H), 2.70-2.65 (*m*, 1H), 2.48-2.45 (*m*, 1H), 2.38-2.31 (*m*, 1H), 2.11-2.07 (*m*, 1H), 1.84-1.81 (*m*, 1H), 1.73-1.53 (*m*, 4H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.4, 139.2, 133.1, 129.4, 128.9, 128.4, 127.4, 70.6, 57.7, 42.9, 30.5, 28.0, 25.1.

2-((4-bromophenyl)(hydroxy)methyl)cyclohexan-1-one (**10i**): Reaction time: 5 days. White solid, 26 mg, yield: 61%, 9:1 d.r., 69% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:9*) δ: 7.48-7.45 (*m*, 2H), 7.21-7.17 (*m*, 2H), 5.34 (*s*, 0.1H, *syn*), 4.75 (*dd*, *J* = 8.7 Hz, *J* = 2.6 Hz, 0.9H, *anti*), 3.97 (*d*, *J* = 2.8 Hz, 0.9H, *anti*), 3.04 (*d*, *J* = 3.3 Hz, 0.1H, *syn*), 2.58-2.52 (*m*, 1H), 2.50-2.46 (*m*, 1H), 2.38-2.32 (*m*, 1H), 2.12-2.07 (*m*, 1H), 1.87-1.78 (*m*, 1H), 1.72-1.64 (*m*, 1H), 1.60-1.50 (*m*, 2H), 1.33-1.25 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.4, 214.8, 140.6, 140.2, 131.6, 131.4, 128.9, 127.7, 121.9, 120.9, 74.3, 70.3, 57.5, 57.1, 42.8, 30.9, 28.1, 27.9, 26.1, 25.0, 24.9.

2-(hydroxy(p-tolyl)methyl)cyclohexan-1-one (**10j**): Reaction time: 7 days. White solid, 137 mg, yield: 39%, 6:1 d.r., 64% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:4*) δ: 7.21-7.18 (*m*, 2H), 7.16-7.14 (*m*, 2H), 5.35 (*d*, *J* = 2.3 Hz 0.2H, *syn*), 4.75 (*d*, *J* = 8.8 Hz, 0.8H, *anti*), 2.63-2.58 (*m*, 1H), 2.50-2.43 (*m*, 1H), 2.40-2.32 (*m*, 4H), 2.10-2.05 (*m*, 1H), 1.79-1.75 (*m*, 1H), 1.69-1.49 (*m*, 3H), 1.32-1.24 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.8, 215.0, 138.6, 138.1, 137.7, 136.7, 129.2, 129.0, 127.1, 125.8, 74.7, 70.7, 57.6, 57.4, 42.8, 31.0, 28.1, 28.0, 26.2, 25.0, 24.9, 21.3.

2-(hydroxy(phenyl)methyl)cyclohexan-1-one (**10k**): Reaction time: 7 days. White solid, 18 mg, yield: 60%, 8:1 d.r., 20% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 2:3*) δ: 7.36-7.23 (*m*, 5H), 5.39 (*s*, 0.4H, *syn*), 4.79 (*d*, *J* = 8.8 Hz, 0.6H, *anti*), 3.95 (*s*, 0.6H, *anti*), 3.01 (*s*, 0.4H, *syn*), 2.65-2.58 (*m*, 1H), 2.50-2.44 (*m*, 1H), 2.41-2.33 (*m*, 1H), 2.10-2.06 (*m*, 1H), 1.86-1.50 (*m*, 4H), 1.35-1.28 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.7, 215.0, 141.6, 141.1, 128.5, 128.3, 128.1, 127.2, 127.1, 125.9, 74.9, 70.8, 57.6, 57.3, 42.8, 31.0, 28.1, 28.0, 26.2, 25.0, 24.9.

2-(hydroxy(naphthalen-2-yl)methyl)cyclohexan-1-one (**10l**): Reaction time: 7 days. White solid, 18 mg, yield: 46%, 7:1 d.r., 62% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:4*) δ: 7.85-7.81 (*m*, 3H), 7.76 (*s*, 1H), 7.50-7.35 (*m*, 3H), 5.57 (*s*, 0.2H, *syn*), 4.97 (*dd*, *J* = 8.8 Hz, *J* = 2.0 Hz 0.8H, *anti*), 4.06 (*d*, *J* = 2.6 Hz, 0.8H, *anti*), 3.16 (*d*, *J* = 3.0 Hz, 0.2H, *syn*), 2.75-2.69 (*m*, 1H), 2.53-2.47 (*m*, 1H), 2.43-2.35 (*m*, 1H), 2.11-2.06 (*m*, 1H), 1.84-1.64 (*m*, 3H), 1.57-1.48 (*m*, 1H), 1.39-1.29 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.7, 215.0, 139.0, 138.4, 133.4, 133.3, 133.2, 132.8, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 126.4, 126.3, 126.2, 126.1, 125.8, 124.8, 124.7, 124.0, 75.1, 70.9, 57.5, 57.2, 42.9, 31.1, 28.1, 27.9, 26.2, 25.0, 24.9.

2-(hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (**10m**): Reaction time: 3 days. White solid, 37 mg, yield: 94%, 8:1 *anti/syn*, 12:1 d.r. (d.r. of the *anti* isomers), 87% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:4*) δ: 8.23-8.21 (*m*, 2H), 7.51-7.50 (*m*, 2H), 5.49-5.47 (*m*, 0.2H, *syn*), 4.92 (*d*, *J* = 8.5 Hz, 0.8H, *anti*), 3.90 (*s*, 0.8H, *anti*), 3.12 (*s*, 0.2H, *syn*), 2.77-2.72 (*m*, 1H), 2.58-2.51 (*m*, 1H), 2.46-2.37 (*m*, 1H), 2.10-2.04 (*m*, 1H), 1.96-1.92 (*m*, 1H), 1.82-1.78 (*m*, 1H), 1.63-1.58 (*m*, 1H), 1.33-1.26 (*m*, 1H), 1.07-1.04 (*m*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.1, 148.5, 147.8, 128.0, 127.9, 126.7, 126.6, 123.8, 123.7, 123.6, 123,5, 74.3, 74.1, 70.5, 70.1, 56.2, 55.9, 53.0, 52.1, 42.2, 41.9, 38.7, 38.3, 36.2, 35.8, 35.6, 33.8, 33.0, 32.9, 31.7, 31.6, 31.5, 26.8, 21.3, 21.2, 18.3, 18.2.

4-ethyl-2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**10n**): Reaction time: 3 days. White solid, 40 mg, yield: 95%, 6:1 *anti/syn*, 15:1 d.r. (d.r. of the *anti* isomers), 83% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 1:4*) δ: 8.22-8.20 (*m*, 2H), 7.51-7.47 (*m*, 2H), 5.48 (*s*, 0.2H, *syn*), 4.92 (*d*, *J* = 8.6 Hz, 0.8H, *anti*), 3.92 (*s*, 0.8H, *anti*), 3.15 (*s*, 0.2H, *syn*), 2.70-2.65 (*m*, 1H), 2.52-2.45 (*m*, 1H), 2.41-2.36 (*m*, 1H), 1.93-1.85 (*m*, 1H), 1.76-1.70 (*m*, 1H), 1.57-1.35 (*m*, 4H), 0.82-0.79 (*m*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.2, 148.5, 147.8, 128.0, 127.9, 126.7, 126.6, 123.8, 123.6, 74.3, 70.5, 70.2, 55.9, 53.1, 52.2, 42.0, 41.8, 38.5, 38.1, 38.0, 33.8, 33.7, 33.2, 33.0, 31.7, 30.6, 30.5, 29.0, 28.7, 28.6, 24.9, 24.8, 12.1, 11.8, 11.7.

2-(furan-2-yl(hydroxy)methyl)cyclohexan-1-one (**10o**): Reaction time: 7 days. White solid, 20 mg, yield: 70%, 4:1 d.r., 72% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 3:7*) δ: 7.39-7.34 (*m*, 1H), 6.34-6.27 (*m*, 2H), 5.27 (*s*, 0.3H, *syn*), 4.83 (*dd*, *J* = 8.4 Hz, *J* = 2.6 Hz, 0.7H, *anti*), 3.88 (*d*, *J* = 3.5 Hz, 0.7H, *anti*), 3.01 (*s*, 0.3H, *syn*), 2.94-2.80 (*m*, 1H), 2.48-2.44 (*m*, 1H), 2.41-2.34 (*m*, 1H), 2.13-2.08 (*m*, 1H), 2.97-2.78 (*m*, 2H), 1.71-1.63 (*m*, 2H), 1.39-1.28 (*m*, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.1, 213.9, 154.8, 153.8, 142.5, 141.6, 110.4, 110.2, 108.1, 106.7, 68.4, 66.9, 55.0, 54.7, 42.8, 42.6, 30.8, 28.0, 27.8, 27.4, 24.9, 24.8.

2-(hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one (**10p**): Reaction time: 7 days. White solid, 6 mg, yield: 17%, 4:1 d.r. ^{1}H NMR (500 MHz, $CDCl_3$) (*syn/anti 3:7*) δ: 7.25-7.21 (*m*, 2H), 6.89-6.86 (*m*, 2H), 5.33 (*s*, 0.3H, *syn*), 4.74 (*d*, *J* = 8.9 Hz, 0.7H, *anti*), 3.92 (*s*, 0.7H, *anti*), 3.80 (*s*, 3H), 2.98 (*s*, 0.3H, *syn*), 2.62-2.54 (*m*, 1H), 2.50-2.42 (*m*, 1H), 2.39-2.32 (*m*, 1H), 2.11-2.06 (*m*, 1H), 1.87-1.75 (*m*, 2H), 1.73-1.50 (*m*, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 215.9, 215.1, 159.4, 158.8, 133.7, 133.3, 128.3, 127.1, 113.9, 113.7, 74.4, 70.6, 57.7, 57.4, 55.4, 42.9, 42.8, 31.0, 28.1, 28.0, 26.3, 25.0, 24.9.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/

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- Highlights

- Preparation of four novel organocatalysts for the solvent-free asymmetric aldol reaction.

- Aldol adducts prepared in up to 95% yield, 1:19 *syn*/*anti* and 98% e.e.

- Sterically bulky aldehydes and substituted cyclohexanones were well tolerated.

- Up to three stereogenic centers formed in a single reaction step.

- Chiral induction through several simultaneous hydrogen bonding interactions.

Design and Preparation of a Novel Prolinamide-based Organocatalyst for the Solvent-free Asymmetric Aldol Reaction

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Declarations of interest: none