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Direct Asymmetric Aldol Reactions Inspired by Two Types of Natural Aldolases: Water-Compatible Organocatalysts and Zn^{II} Complexes

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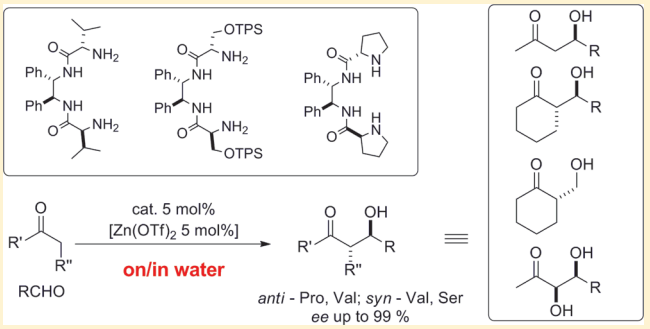
Supporting Information

ABSTRACT: In this article the utility of water-compatible amino-acid-based catalysts was explored in the development of diastereo- and enantioselective direct aldol reactions of a broad range of substrates. Chiral C_2-symmetrical proline- and valine-based amides and their Zn^{II} complexes were designed for use as efficient and flexible chiral catalysts for enantioselective aldol reactions in water, on water, and in the presence of water. The presence of 5 mol % of the prolinamide-based catalyst affords asymmetric intermolecular aldol reactions between unmodified ketones and various aldehydes to give *anti* products with excellent enantioselectivities. We also demonstrate aldol reactions of more demanding substrates with high affinity to water (i.e., acetone and formaldehyde). Newly designed serine-based organocatalyst promoted aldol reaction of hydroxyacetone leading to *syn*-diols. For presented catalytic systems organic solvent-free conditions are also acceptable, making the elaborated methodology interesting from a green chemistry perspectives.



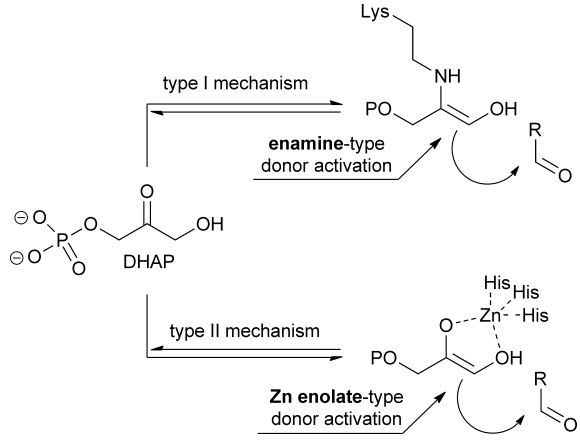
1. INTRODUCTION

The aldol reaction is a key carbon−carbon bond-forming tool for organic synthesis and bio-organic transformations in nature.[1] The ability to control the enantioselectivity of the newly generated stereogenic centers has established this reaction as the principal chemical transformation for the stereoselective construction of simple β-hydroxy carbonyl building blocks and more complex polyol architectures.[2] The aldol reaction is also crucial for the biosynthesis of carbohydrates, keto acids, and some amino acids.[3] The reaction is originally catalyzed by enzymes using either the enamine (type I aldolases) or metal enolate (type II aldolases) mechanisms (Scheme 1).

Type I aldolases function via an enamine mechanism, in which an enzyme lysine residue reacts with the donor component (at the Scheme 1 dihydroxyacetone phosphate, DAHP) to generate an enamine in the active site. In the latter, a metal cofactor is bound in the enzyme active site (usually Zn), which acts as a Lewis acid to activate substrate. This acidifies the α-proton, allowing for facile generation of zinc enolate in the active site.

These biological processes have provided a template for the development of small molecule catalysts activating substrates using *direct aldol* reaction strategy.[4] While virtually all the biochemical aldol reactions use unmodified donors and acceptors and take place in an aqueous environment, the chemical domain of the aldol addition has mostly relied on prior transformation of carbonyl substrates, and the whole process traditionally is carried out in anhydrous solvents.

Scheme 1. Mechanism of Type I and II Aldolases



Application of catalytic amounts of various nonenzymatic chiral promoter to control the aldol reactions is undoubtedly a big achievement of modern organic chemistry.[5] Another challenge is to find a catalyst capable of activating the donor and the acceptor carbonyls simultaneously in water environment.[6] Two obvious biomimetic strategies have been employed to follow the aldolases' mode of action in aqueous media: (1) organocatalysts,[7] including modified amino acids and small

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peptides, acting as type I aldolases, and (2) metal-catalyzed aldol reactions[8] generally based on zinc complexes. Although small organic molecules and metal-catalyzed direct aldol reactions in organic solvents have been developed with a great deal of success, their catalytic efficiency and substrate scope in aqueous media have so far been limited.

Proline catalyzes direct aldol reactions with high enantioselectivity in polar organic solvents such as DMSO and DMF, but in the presence of water[9] or a buffer solution, nearly racemic products were obtained.[10] After initial application of catalytic antibodies,[11] nornicotine[12] and some other organocatalysts have been tested in water environment.[13] It has been also demonstrated by Janda's[12] and Barbas'[9] groups that the enamine, which had been considered to be easily hydrolyzed in the presence of water, is in fact generated and reacts with an electrophile to afford the aldol under aqueous conditions.

In 2004, Pihko recorded significantly higher yields on addition of water to an intramolecular aldol reaction catalyzed by proline in homogeneous water/DMF solution.[14] Further efforts have been made to develop efficient organocatalysts for asymmetric intermolecular aldol reaction in water: proline,[15] various proline derivatives,[16] and some other amino acids[17] were used as catalysts in aqueous−organic solvents with some success. For the catalysts operating in water *without* organic cosolvents, only moderate enantioselectivities were initially observed.[18]

In 2006 Barbas et al. carried out a highly enantioselective direct aldol reaction catalyzed by a proline-based hydrophobic diamine in water.[19] This enantioselective methodology was promising only for cyclic ketones while acyclic substrates gave only moderate enantioselectivities. Simultaneously, Hayashi and coworkers reported that a siloxyproline catalyzed highly enantioselective aldol reaction in water by using only 1 mol % of the organocatalyst.[20] The presented catalyst works in biphasic medium and failed to provide any product if one of the partners was water miscible. More recently, Barbas III hypothesized that a small organic catalysts with appropriate hydrophobic groups assembled with the hydrophobic reactants in water and sequestered the transition state from water. As a result, the outcome of the reaction should be similar to that performed in organic solvents.[21] Further examples of highly enantioselective aldol recations in water are known; the efficient and nearly quantitative reaction of cyclohexanone in a presence of large amount of water was also described.[22]

The above-mentioned catalysts have the limitation of giving moderate enantioselectivity with a water-miscible ketone such as acetone or hydroxyacetone (HA), a highly desirable substrate from a conceptual and synthetic point of view. Therefore, there was a great need for a chiral organocatalysts that could overcome these drawbacks. To solve this problem Singh et al. developed prolinamide catalyst bearing a nonpolar *gem*-diphenyl group that works very efficiently for acetone in water.[23] Nevertheless, application of water-soluble substrates still remains unsolved while most published examples of organocatalysts activate only cyclic ketones in the presence of a small amount of water. More flexible catalytic systems in the field are still elusive.

Recent progress in the area[24] has initiated constructive discussion on the role and practical merits of water as a solvent.[25] Water and water-based reactions were debated with regard to terminology (i.e., whether a reaction is carried out "in water", "in the presence of water", or "in the presence of a large excess of water").[26] This discussion showed also increased interest in the search for organic catalysts that can promote effectively not only biphasic reaction of cyclic ketones but also reactions in homogeneous water solution for a broad range of substrates.[27] Better understanding of such a process is an important issue in the context of general asymmetric synthesis.

The parallel field of metal-catalyzed enantioselective direct aldol reaction mimicking type II aldolases in water has afforded less satisfactory results. The first application of an *in situ* generated zinc complex with amino acid ester ligands (TyrOEt) was presented in 1985.[28] The readily available catalyst, although reactive, was unselective and led to racemic products by direct condensation of acetone with aromatic aldehydes. First example of an asymmetric direct aldol reaction of acetone in water was described by Darbre et al.[29] Zinc complexes of a range of amino acids were tested in the aldol reaction of acetone and 4-nitrobenzaldehyde with the best results observed for proline, lysine, and arginine. Enantiomeric excesses of up to 56% could be obtained with only 5 mol % of $Zn(Pro)_2$ at room temperature. This reaction was conducted in homogeneous acetone/water solution (1:2), making ketone not only the reactant but also the solvent. Again, the aldol reaction catalyzed by zinc complexes is regio- and stereoselective with hydroxy- and dihydroxyacetone but leads unfortunately to racemic hydroxyaldols. The authors suggested that the applied catalyst forms enamine species with acetone, but with dihydroxyacetone Zn-enolate formation is preferred.[30] More recently, Aoki reported interesting mechanistic studies of catalysts consisting of chiral amino acids and Zn−cyclene complex.[31] Aldol reactions of acetone and unprotected α-hydroxyketones such as hydroxy- and dihydroxyacetone were catalyzed to give adducts with only moderate ee values (up to 45%).

Continuous development of asymmetric aldol reaction in/on water seems to be rational, as aqueous homogeneous and biphasic catalysis is one of the most promising strategies toward more economical and green processes.[32] Undoubtedly, more promising application of naturally occurring hydrophilic substrates would be a great achievement in the field. In 2007 we presented our preliminary studies on application of bisprolinamide zinc complex for direct asymmetric aldol reaction in aqueous media.[33] The presented catalyst, although active for cyclic and acyclic ketones, lost some selectivity for reactions performed with equimolar ratios of carbonyl partners in pure water. Herein we report a comprehensive overview on the use of simple α-amino acids derivatives as practical, highly efficient, and substrate-flexible catalysts for direct asymmetric aldol reaction on/in water. The presented amino-acid-equipped ligands are tunable catalysts for direct aldol addition in the presence of a large amount of water without any additives (organocatalyst) and also as a zinc complexes.

2. RESULTS AND DISCUSSION

2.1. Asymmetric Aldol Reaction Catalyzed by Zn Complexes. Scope and Limitations. It was shown in our previous work that direct aldol reaction between acetone and 4-nitrobenzaldehyde can be efficiently promoted in an aqueous media using C_2-symmetric Zn-bisprolinamide **2a**.[33] Catalyst design was based on an analogy to type II aldolases in which the zinc ion is tightly coordinated by three histidine residues in the reaction active site.[34] In our search for the best catalysts, we introduced C_2-symmetry based on chiral (**2**, **3**) and achiral scaffolds (**1**). Thus, based on literature protocols[35] we synthesized bisprolinamides **1**−**3**, expanding the family by diastereo- and enantiomers of known compounds (Scheme 2).

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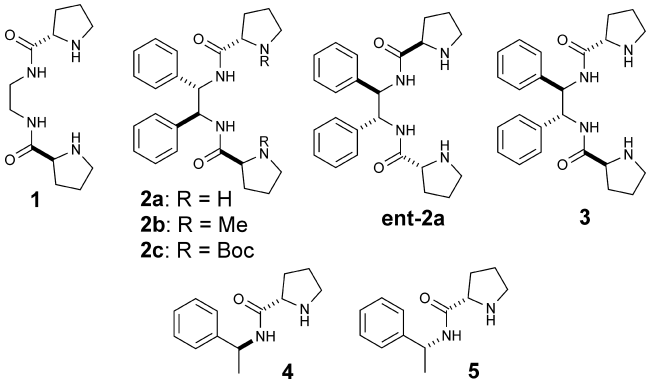
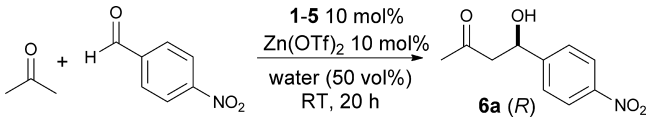
Scheme 2. Bisprolinamide Catalysts Used at the Initial Stage of the Study



We tested also zinc complexes of monoprolinamides **4** and **5** in order to compare efficiency of catalysts with C_1- and C_2-symmetry.

The reaction of acetone with 4-nitrobenzaldehyde was explored as a catalyst test. The same reaction has been explored in previous papers on the same subject leading to desired aldol **6a** with enantiomeric excesses of up to 56%.[29] Application of all tested ligands as organocatalysts to the aldol reaction led to promising results, and the condensation proceeded efficiently in aqueous medium in all cases, yet observed ee's were poor.[33] However, addition of zinc trifluoromethanesulfonate increased the selectivity as reflected in higher enantioselectivities (Table 1). The best results with respect to yield and ee were observed with catalyst **2a** and $Zn(OTf)_2$ as additive (Table 1, entry 2). The addition of Zn-salt increased the enantioselectivity from 6% to 60%.[33] We did not observe the formation of aldol **6** in the presence of $Zn(OTf)_2$ and (*S*)-proline (1:2) under similar reaction conditions. Interestingly, a C_2-symmetric bisprolinamide with two prolinamide moieties has been proved to be a better catalyst's part component than its prolinamide analogues **4** and **5** (Table 1, entries 2 vs 6, 7).

Table 1. Screening of Efficient Catalysts in the Direct Asymmetric Aldol Reaction of Acetone with 4-Nitrobenzaldehyde



entry	catalyst	yield (%)[a]	ee (%)[b]
1	**1**/$Zn(OTf)_2$	90	24
2	**2a**/$Zn(OTf)_2$	92	60
3	**2b**/$Zn(OTf)_2$	0	
4	**2c**/$Zn(OTf)_2$	0	
5	**3**/$Zn(OTf)_2$	98	27
6	**4**/$Zn(OTf)_2$	75	39
7	**5**/$Zn(OTf)_2$	93	16
8	**2a**/$Zn(OTf)_2$	87[c]	86

[a]Isolated yield. Conditions: catalyst (10 mol %), $Zn(OTf)_2$ (10 mol %), 4-nitrobenzaldehyde (0.50 mmol) in acetone/water (1/1, 2 mL) at rt for 20 h. [b]Enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AS-H). [c]Conditions: **2a** (5 mol %), $Zn(OTf)_2$ (5 mol %), 4-nitrobenzaldehyde (0.50 mmol) in acetone/water (9/1, 1 mL) at rt for 20 h

We next checked the solvent effect on this aldol reaction employing zinc complex with ligand **2a** as a catalyst; the results are summarized in a previous paper.[33] In water alone the zinc complex gave the (*R*) enantiomer in 36% ee. We were delighted to find that the reaction without any organic cosolvents proceeded well when 5 mol % of the catalyst was applied (Table 1, entry 8). In this case desired aldol was isolated in high yield with 86% enantiomeric excess, after reaction at room temperature.

The scope of this aldol reaction using diamide **2a**/$Zn(OTf)_2$ catalyst in the presence of large amount of water was examined, and the results are summarized in Table 2. Aldehyde acceptors with electron-withdrawing substituents show higher reactivity. In all cases, however, the reaction proceed smoothly at room temperature, and enantioselectivity was good to high (entries 1−6). Both excellent enantioselectivity and *anti*-selectivity were obtained when cyclohexanone was employed (entries 8−14). The aldol reactions of *o*- and *m*-substituted aldehydes show higher selectivity than that of *p*-substituted donors.

On the basis of presented findings it should be noted that the large excess of water does not influence on the reaction results. The developed zinc-based chiral catalyst seems efficient and enantioselective system for aqueous aldol reaction, maintaining high selectivity for noncyclic ketones without any organic cosolvents.

2.2. Enantioselective Synthesis of (*R*)-Lipoic Acid Precursor. Previously presented aldol methodology can be also efficiently applied for the crucial step in enantioselective synthesis of biologically relevant molecules. (*R*)-α-Lipoic acid (**7**) plays an important role as a protein-bound transacylating cofactor of several multienzymatic α-keto acid dehydrogenase complexes.[36] Since its isolation, (*R*)-α-lipoic acid has attracted great attention because of its diverse biological functions. It is an important growth factor, acting as a coenzyme in many biological processes found in animal tissues, plants, and microorganisms.[37] In addition, it serves as an effective scavenger for reactive oxygen species (ROS),[38] which have been implicated in a number of pathological conditions such as carcinogenesis, inflammation, ischemia-reperfusion injury, and aging. It has been reported that naturally occurring (+)-(*R*)-α-lipoic acid (**7**) and its derivatives possess more potent anti-HIV and antitumor activities than its (*S*)-enantiomer.[39] Few asymmetric synthesis of this molecule have been presented[40] including organocatalytic approach by using an L-proline-catalyzed cross-aldol reaction as the key step. It was shown that the target molecule could be attained from lactone **8** (Scheme 3.) This disconnection raised a synthetic challenge related to the installation of the stereogenic centers in precursor lactone **9**. This, in turn resulted from L-proline-promoted cross-aldol reaction between cyclohexanone and benzyloxyacetaldehyde.[40b]

We found it interesting to examine the generality of previously elaborated zinc catalyst, as organocatalytic cross-aldol reactions between cyclohexanone and desired aldehyde created a significant challenge since the highly active aldehydes readily undergoes self-aldol reaction. The results of aldol reaction are summarized in Table 3.

With 20 mol % of proline, the reaction of cyclohexanone and aldehyde **10** finished in 16−20 h with perfect ee and (95:5) diastereoisomers ratio (Table 3, entry 1). The use of ketone as a reaction medium led to a dramatic improvement in the yield of the cross-aldol reaction.[40b] Application of **2a**/$Zn(OTf)_2$ in

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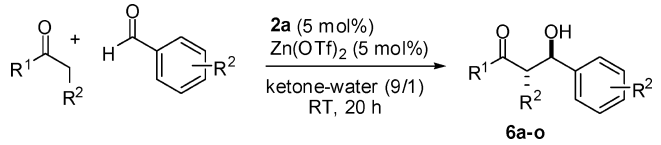
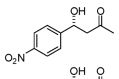
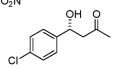
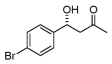
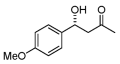
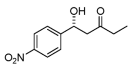
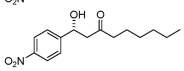
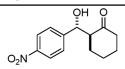
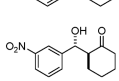
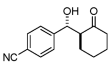
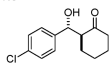
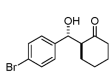
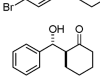
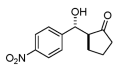
Table 2. Direct Catalytic Asymmetric Aldol Reaction in the Presence of Water Catalyzed by 2a/Zn(OTf)$_2$ (5 mol %): Substrate Scope



6a-o

entry	product	aldol	yield (%)[a]	*anti*/*syn*[b]	ee *anti* (%)[c]
1		**6a**	88	-	88[d]
2		**6b**	80	-	90
3		**6c**	83	-	88
4		**6d**	77	-	90
5		**6e**	21	-	86
6		**6f**	54	-	88
7		**6g**	33	-	84
8		**6h**	98	95/5	94
9		**6i**	56	98/2	97
10		**6j**	71	98/2	97
11		**6k**	94	96/4	93
12		**6l**	56	98/2	94
13		**6m**	56	96/4	96
14		**6n**	46	98/2	94
15		**6o**	82	44/66	46 (*anti*) 18 (*syn*)

[a]Yield refers to combined yield of isolated diastereomers. Conditions: prolinamide catalyst **2a** (0.025 mmol, 5 mol %), Zn(OTf)$_2$ (0.025 mmol), aldehyde (0.50 mmol) in ketone/water mixture (9/1, 1 mL) at rt for 20 h. [b]Diastereoselectivity was determined by HPLC and ^{1}H NMR analysis of the isolated diastereomers. [c]Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H). [d]This system seems to be selective for the formation of the (*R*) configuration. All isolated aldol adducts were found in the (*R*)- (entries 1−7) and (2*S*,1′*R*)-stereochemistry (entries 8−15).

the presence of water delivered essentially the same results, while only 5 mol % of catalyst loading was necessary. An obvious advantage of this strategy was much less ketone loading being necessary for obtaining the same yield of aldol **11**. Interestingly, the same catalyst failed to react without water additive. Thus obtained compound **11** was transformed into key intermediate **9** in 65% yield using a literature protocol.[40b]

2.3. Effect of the Amount of Ketones and Water. Previously presented methodology, although highly substrate flexible, suffers from a large excess of ketone that should be used for obtaining reasonable yield. When an expensive ketone is used in large excess, it is not reassuring for the direct aldol reaction with atom-economical aqueous green chemistry. The use of less volatile ketones in large excess, for example cyclohexanone, complicates the reaction workup and final product purification. On the other hand, ideal water-compatible catalyst should operate in high excess of water, even used as a solvent. The essential role of water was observed when the reaction promoted by **2a**/Zn-salt was carried out in pure cyclohexanone. In this case only a trace of product was isolated (Table 4, entry 1). Addition of water (10 vol %) resulted in essential increasing of reactivity and selectivity. In a reaction conducted at 0 °C the ee reached smoothly 98% with perfect diastereoselectivity and reasonable reactivity of the catalytic system with only 5 mol % catalyst loading (Table 4, entry 2). Application of zinc trifluoroacetate as an additive showed similar selectivity in the presence of 10 vol % of water (entries 2

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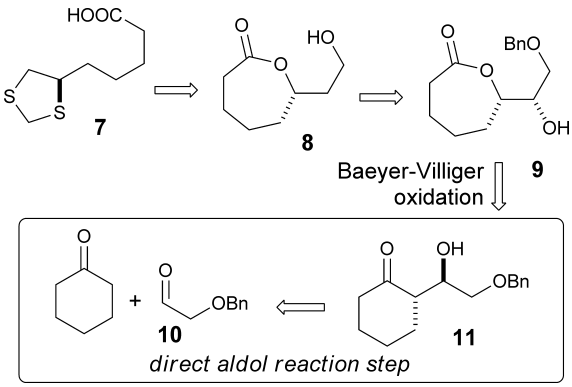
Scheme 3. Crucial Aldol Step in the Synthesis of (*R*)-Lipoic Acid



vs 4), while both catalysts lost selectivity in huge amounts of water (entries 5 and 6).

Thus, the reaction selectivity was greatly affected with increasing amount of water in the reaction mixture. This unwelcome tendency can be overcome by application of ytterbium salt[33] or by application of improved zinc complex with more water-tolerant ligand **12**. Whereas in the natural enzyme the enamine is formed at the lysine residue in the active site,[3] most presented catalysts contain a cyclic proline motif for this purpose. Studies of enantioselective organocatalytic reactions promoted by primary amino acids and their derivatives[41] provided interesting and fresh results.[42] The most promising applications of siloxythreonine and siloxyserine must be seen, however, as reactions "in the presence of water" rather than "in water".[22b,c] Nevertheless, we applied newly designed bisvalinamide ligand **12**, which turned out to be more water-compatible when compared to the proline derivative. The reaction proceeds smoothly in a large excess of water to provide excellent selectivity with various aldehydes (Table 4, entries 7−11). Organic cosolvent additive was not necessary for obtaining good yield and high enantioselectivities under presented conditions.

2.4. Direct Asymmetric Hydroxymethylation of Ketones in Aqueous Systems. Hydroxymethylation reactions represent one of the most useful one-carbon extension methods,[43] but the use of formaldehyde as a C1-unit in direct catalytic asymmetric aldol reactions is surprisingly rare, possibly due to its high reactivity, high affinity to water, and symmetrical structure. The direct use of commercially available aqueous formaldehyde (formalin) solution gives the safest and most economically attractive reaction conditions. Whereas asymmetric aqueous hydroxymethylation of an enolate component with formaldehyde is known,[44] the direct use of ketones instead of silicon enolates in water still needs further investigations. Recently, two examples of organocatalytic asymmetric hydroxymethylation using formalin in the presence of a small amount of water were reported.[45] In both cases, the chemical yields were moderate, and the substrate scope was limited to a single example, cyclohexanone, which is insoluble in pure water.

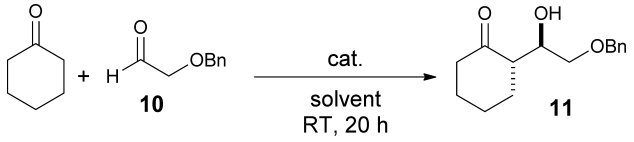
To improve the flexibility of the elaborated catalytic system we focused on the direct aldol reaction of formaldehyde promoted by a Zn complex of prolinamide **2a**. Optimization studies using cyclohexanone and formalin are summarized in Table 5. To start from an organocatalytic protocol, cyclohexanone (1.5 mmol), aqueous formaldehyde (0.75 mmol), and 10 mol % of catalyst **2a** were mixed in DMSO (Table 5, entry 1). α-Hydroxymethyl ketone **13** was isolated in 10% yield and 42% ee. Unfortunately, the use of a homogeneous aqueous solution affected the enantioselectivity. Although the reaction proceeded sluggishly under organocatalytic protocols (entries 1−4), the use of a catalytic amount of zinc triflate resulted in an improved yield and enantioselectivity (entries 5, 6). The use of an ethanol/water solution instead of THF/water mixtures improved further the reaction. As far as we are aware, there are no other examples in which this reaction proceeds with high enantioselectivity in aqueous solution, with all of the reagents and catalyst dissolved homogeneously in the reaction mixture. The reaction in brine or in water is less efficient (entries 7, 8), but the yield of hydroxymethylation in pure water can be further improved by the use of an ultrasound bath (entry 9).

The reaction of cyclohexanone and formaldehyde was carried out in pure water (1 mL) to generate the desired aldol in 74% yield and 95% ee. Sonication enables the rapid dispersion of ketone substrate on the water surface, allowing better contact between water and reactants. The use of ultrasound as a means of accelerating reactions is an important technique and one that is rapidly developing for green processes.[46]

Comparison of the HPLC analysis, on a chiral stationary phase, of the benzoyl derivative of the product with that reported in the literature[44a] revealed that applied proline-based catalyst provided (*S*)-2-hydroxymethyl cyclohexanone.

The presented methodology is acceptable for other cyclic ketones (cyclopentanone: 58%, 98% ee, cycloheptanone: 59%, 93% ee, in homogeneous solution of EtOH/water, 9/1).[47] Recently, an excellent example of a metal-assisted direct hydroxymethylation in water was presented by Kobayashi,[48] but the

Table 3. Cross Aldol Reaction between Cyclohexanone and Benzyloxyacetaldehyde



entry	catalyst	substrates	water	yield (%)[a]	ee (%)[b]
1	L-proline (20 mol %)	ketone (10 mL) **10** (3.3 mmol)		65	95 (de 90)
2	**2a**/Zn(OTf)$_2$ (5 mol %)	ketone (0.9 mL) **10** (3.3 mmol)		nd	
3	**2a**/Zn(OTf)$_2$ (5 mol %)	ketone (0.9 mL) **10** (3.3 mmol)	0.1 mL	66	95 (de 94)

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AS-H).

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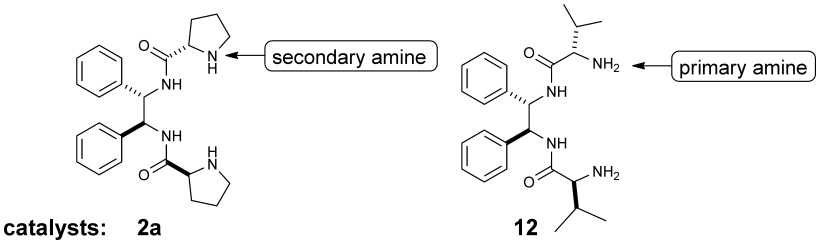
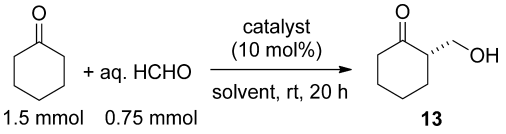
Table 4. Direct Catalytic Asymmetric Aldol Reaction in the Presence of Larger Excess of Water without Organic Cosolvents



entry	R-C_6H_4CHO, R =	catalyst	ketone/water	temp (°C)	yield (%)[a]	*anti*/*syn*[b]	ee *anti* (%)[c]
1	*p*-NO_2	**2a**/$Zn(OTf)_2$	cyclohexanone	rt	tr		
2	*p*-NO_2	**2a**/$Zn(OTf)_2$	cyclohexanone/water (9/1)	0	93	98/2	98
3	*p*-NO_2	**2a**/$Zn(OTf)_2$	cyclohexanone/water (1/1)	rt	86	87/13	80
4	*p*-NO_2	**2a**/$Zn(OTFA)_2$	cyclohexanone/water (9/1)	rt	99	98/2	94
5	*p*-NO_2	**2a**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	86	8/2	57
6	*p*-NO_2	**2a**/$Zn(OTFA)_2$	cyclohexanone (5 equiv) in water	rt	85	82/18	66
7	*p*-NO_2	**12**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	74	9/1	97
8	*m*-NO_2	**12**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	85	88/12	98
9	*o*-NO_2	**12**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	45	99/1	99
10	*p*-Cl	**12**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	41	8/2	99
11	H	**12**/$Zn(OTf)_2$	cyclohexanone (5 equiv) in water	rt	27	9/1	98

[a]Yield refers to combined yield of isolated diastereomers. Conditions: catalyst **2a**/**12** (0.025 mmol, 5 mol %), metal salt (0.025 mmol, 5 mol %), aldehyde (0.50 mmol) in cyclohexanone/water (1 mL) or catalyst **2a**/**12** (0.025 mmol, 5 mol %), metal salt (0.025 mmol. Five mol %), aldehyde (0.50 mmol), cyclohexanone (260 μL, 2.50 mmol) in water (1 mL). [b]Diastereoselectivity was determined by HPLC and ^{1}H NMR analysis of the isolated diastereomers. [c]Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H).

Table 5. Direct Catalytic Aldol Reaction of Cyclohexanone with Formaldehyde



entry	catalyst	solvent	yield (%)[a]	ee (%)[b]
1	**2a**	DMSO	10	42
2	**2a**	THF/H_2O (9/1)	25	20
3	**2a**/TFA	THF/H_2O (9/1)	23	rac
4	**2a**/TfOH	THF/H_2O (9/1)	tr	
5	**2a**/$Zn(OTf)_2$	THF/H_2O (9/1)	39	92
6	**2a**/$Zn(OTf)_2$	EtOH/H_2O (9/1)	55	94
7	**2a**/$Zn(OTf)_2$	brine	25	90
8	**2a**/$Zn(OTf)_2$	H_2O	25	95
9	**2a**/$Zn(OTf)_2$	H_2O[c]	74	95

[a]Isolated yield. The reaction was performed by employing formalin (0.75 mmol, 37% in water), cyclohexanone (1.5 mmol), catalyst **2a** (10 mol %), and solvent (1 mL). Additives: $Zn(OTf)_2$ (10 mol %), TFA (20 mol %). [b]Determined by HPLC analysis of the benzoate ester on a chiral phase (Daicel OD-H column). [c]The reaction was performed in 0.5 mL of water at rt for 10 h in an ultrasound bath.

applied catalytic system seems to be also limited to cyclic ketones.

2.5. Mimicking Type I Aldolases by Organocatalytic Aldol Reactions in Water. In the previous paragraph we showed that direct hydroxymethylation of cyclic ketones needs prolinamide ligand supported by Zn-salt, while a protonated ligand failed to react under the same aqueous conditions (Table 5). However, a C_2-symmetric bisprolinamide with two L-amino acid moieties has been found previously to be a promising catalyst for direct aldol reaction of/in dry acetone with more than doubled reactivity and better asymmetric induction than its monoprolinamide counterpart.[35b] Molecules of amides **2a** and **12** are insoluble in water and, according to Hayashi, can support reactions "in the presence of water". Nevertheless, we decided to test activity of organocatalyts **2a** and **12** in the presence of larger amount of water assuming their high selectivity. To test this hypothesis we focused only on reactions of 5-fold excess of ketone to aldehyde in the presence of large excess of water. First, we compared results of the reaction between cyclohexanone (5 equiv) and 4-nitrobenzaldehyde in water (1 mL) catalyzed by both prolinamide **2a** and valinamide **12** with various acid-type additives (TFA, TfOH, AcOH). Acetic acid showed a little worse selectivity, while triflic acid decreased the high reactivity of bisprolinamide. The best results observed for trifluoroacetic acid additive are summarized in Table 6.

While only valinamide zinc complex was highly selective under similar conditions in water (Table 4), both prolinamide and valinamide promoted diastereo- and enantioselective aldol reaction when protonated by trifluoroacetic acid (entries 2 and 4). High enantioselectivity was observed for valinamide **12** without any additives yet observed diastereoselectivity was disappointing (entry 3). Better balance between yield and selectivity was achieved by using protonated prolinamide, and this catalyst was used for further testing of reactions' scope. The best results with respect to yield, diastereoselectivity, and enantioselectivity were observed with **2a** and TFA as additive. Good levels of ee and excellent diastereoselectivities were maintained in water at around 0 °C (entry 5). For practical reasons the catalyst loading was raised to 10 mol % and longer reaction times were needed (entries 6–8). The same good yield and selectivity were observed for far less reactive benzaldehyde (entry 9) when more ketone was used. Protonated organocatalyst **2a** and **12** seem to be less selective for acyclic ketones, leading to a good level of ee only for acetone (entry 10).

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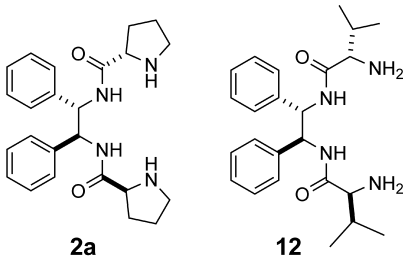
Table 6. Organocatalytic Asymmetric Aldol Reaction in the Presence of Larger Excess of Water

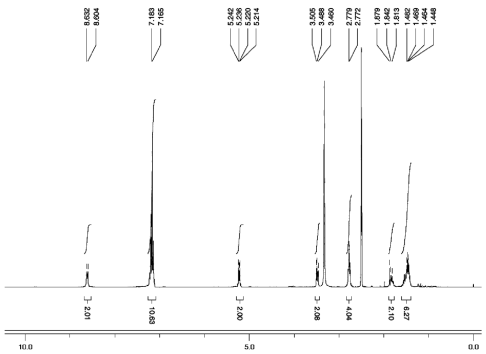


entry	R-C_6H_4CHO, R =	catalyst	ketone/water	temp (°C)	yield (%)[a]	*anti*/*syn*[b]	ee *anti* (%)[c]
1	*p*-NO_2	**2a**/-	cyclohexanone (5 equiv) in water	rt	99	85/15	72
2	*p*-NO_2	**2a**/TFA	cyclohexanone (5 equiv) in water	rt	89	93/7	91
3	*p*-NO_2	**12**/-	cyclohexanone (5 equiv) in water	rt	86	75/25	95
4	*p*-NO_2	**12**/TFA	cyclohexanone (5 equiv) in water	rt	65	93/7	92
5	*p*-NO_2	**2a**/TFA	cyclohexanone (5 equiv) in water	0	20	99/1	95
6	*p*-NO_2	**2a**/TFA	cyclohexanone (5 equiv) in water	0[d]	89	96/4	95
7	*p*-CN	**2a**/TFA	cyclohexanone (5 equiv) in water	0[d]	94	96/4	93
8	*p*-Cl	**2a**/TFA	cyclohexanone (5 equiv) in water	0[d]	45	98/2	95
9	H	**2a**/TFA	cyclohexanone/water (9/1)	rt[e]	76	98/2	94
10	*p*-NO_2	**2a**/TFA	acetone/water (9/1)	rt	90		90

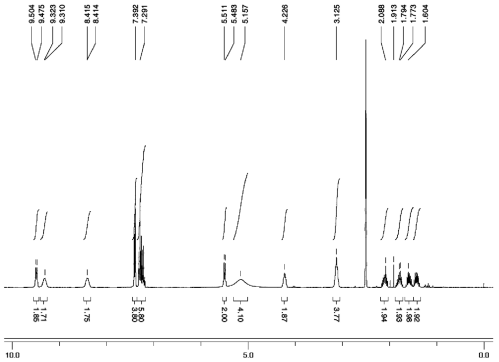
[a]Yield refers to combined yield of isolated diastereomers. Conditions: catalyst **2a**/**12** (0.025 mmol, 5 mol %), additive (if used, 0.050 mmol, 10 mol %), aldehyde (0.50 mmol), cyclohexanone (260 μL, 2.50 mmol) in water (1 mL). [b]Diastereoselectivity was determined by HPLC and ^{1}H NMR analysis of the isolated diastereomers. [c]Determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H). [d]Reaction time 70 h, catalyst loading 10 mol %. [e]Reaction time 40 h.

Scheme 4. NMR Studies of Ligand 2a

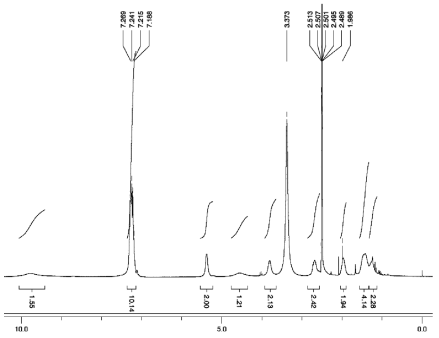
i) ligand **2a** in DMSO-d_6



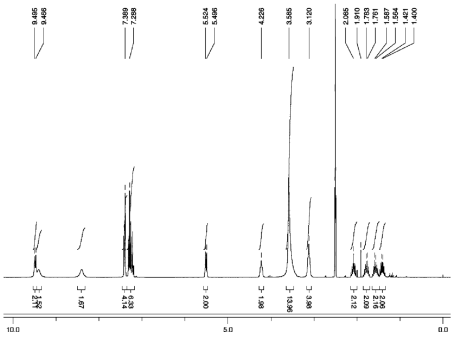
ii) ligand **2a** and TFA (1:2) in DMSO-d_6



iii) ligand **2a** and $Zn(OTFA)_2$ (1:1) in DMSO-d_6



iv) ligand **2a** and $Zn(OTFA)_2$ and TFA (1:1:2) in DMSO-d_6



2.6. Insight into Zn-Based Catalyst Structures. To shed light on the possible structure of the catalysts and the catalytic action of species formed *in situ*, we gained insight into the NMR spectra of H^+ salt and Zn^{II} complexes with representative examples of both classes of tested ligands. We first examined the ^{1}H NMR spectra of proline-based catalyst **2a** (Scheme 4). After addition of 2 equiv of trifluoroacetic acid, NMR spectra clearly changed. The most interesting signals

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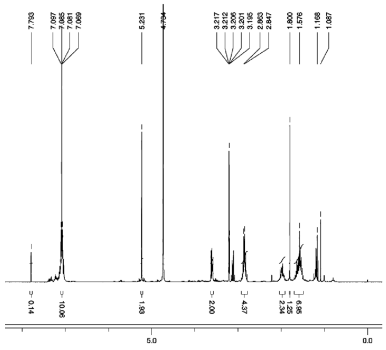
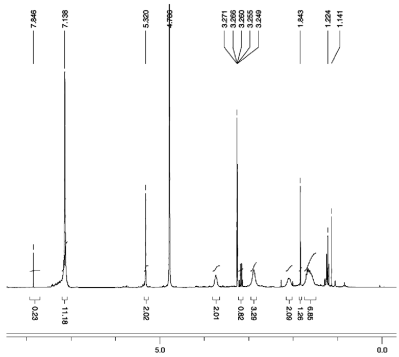
Scheme 5. NMR Studies of Ligand 2a

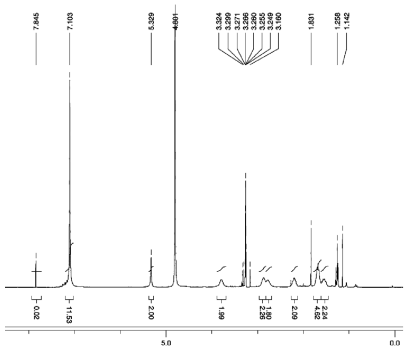
i) ligand **2a** in CD_3OD



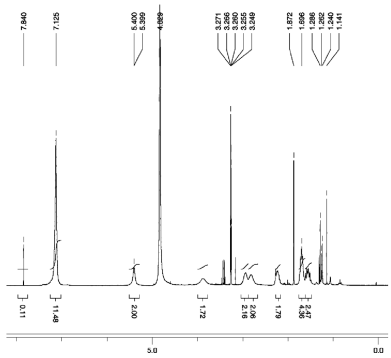
ii) ligand **2a** and $Zn(OTFA)_2$ (1:0.1) in CD_3OD



iii) ligand **2a** and $Zn(OTFA)_2$ (1:1) in CD_3OD



iv) ligand **2a** and $Zn(OTFA)_2$ (1:2) in CD_3OD



were those of two diastereotopic protons at the pyrrolidine nitrogen (δ 8.41 and 9.32 ppm). Addition of 1 equiv of $Zn(OTFA)_2$ resulted in the broadening of most signals. Such a change must have resulted from a restrained rotation in the ligand core and arms. It is noteworthy that amide protons still appeared in spectra as broad signals, suggesting coordination of Zn to the carbonyl group rather than to the amide nitrogen (with possible deprotonation). Addition of TFA to previously formed complex (*iii*) resulted in the formation of protonated structure (*iv*), almost identical in NMR experiment to that formed by direct protonation (*ii*). This suggests an essential role of pyrrolidine nitrogen coordination to zinc at the initially formed complex.

Further, we tested ligand structure by using better soluble zinc trifluoacetate in CD_3OD solution (Scheme 5). Interestingly, strong change in spectra was observed with only 0.1 equiv of Zn-salt. This suggest rather fast metal–ligand exchange in the dynamic system at on the NMR experiment time scale. Saturation, if any, was observed when 2.0 equiv of $Zn(OTFA)_2$ was added, indicating a (2:1) stoichiometric complexation of metal salt to ligand.

The ^{1}H NMR spectra of a valine-composed complex showed features similar to those observed for the proline-based complex (Scheme 6). In the titration experiment, saturation was observed for a (2:1) stoichiometric complexation of metal salt to ligand **12**. For this ligand, however, symmetrical structure was observed, indicating a better-defined complex at room temperature.

For both ligands **2a** and **12**, the complexation of zinc to carbonyl oxygen and nitrogen of amine rings is expected on the basis of presented NMR experiments. So far we have used a complex with (1:1) ligand–metal ratio as an aldol reaction catalyst, but we could not neglect such a result suggesting a possible (1:2) ratio of ligand–zinc complex. Thus the loading amount of $Zn(OTf)_2$ in the reaction was also investigated (Table 7).

The use of 5 mol % of zinc salt (1:1 with **2a**) seemed best for the reaction (Table 7, entry 2). Although lower loading of $Zn(OTf)_2$ decreased both yield and selectivity, no improvement was detected when more than 5 mol % of additive was used (entry 5).

To gain insight into the sense of the asymmetric induction of the aldol reaction resulting from the elaborated procedure, we compared the optical rotation and results from HPLC analysis of the obtained aldol with published data. The absolute configuration of aldol **6a** was determined as (4*R*) by a comparison of the optical rotation of **6a** with those of compounds prepared in our laboratory using (*S*)-proline-organocatalyst and the protocol initially described by List. Comparison of optical rotation and HPLC analysis unambiguously showed the same absolute configuration of both aldols prepared using proline and proline-based **2a**.[49]

The new catalyst incorporates a metal center that can act as a Lewis acid in water and mimics the mode of action of type II aldolases (Scheme 7). On the other hand, the complex could also form an enamine intermediate (**II**), in analogy to type I aldolases. The fact that proline alone is not an efficient catalyst supports only the expectation that enamine formation is unfavorable under the aqueous reaction conditions. The zinc complex gave the (*R*) enantiomer of the aldol product in excess, and with proline alone, the same (*R*) enantiomer was also predominant. Thus, we postulate similar mechanism involving organocatalytic

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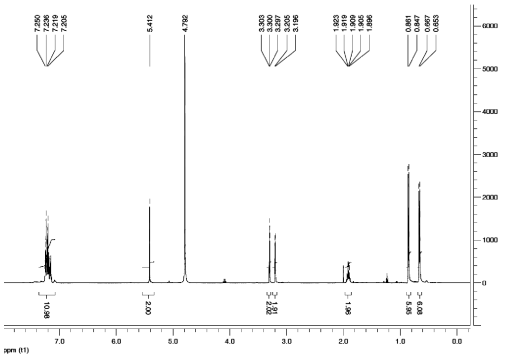
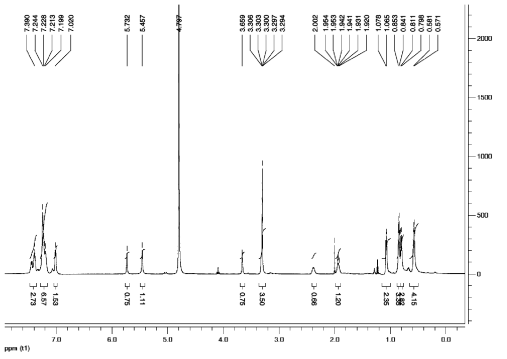
Scheme 6. NMR Studies of Ligand 12

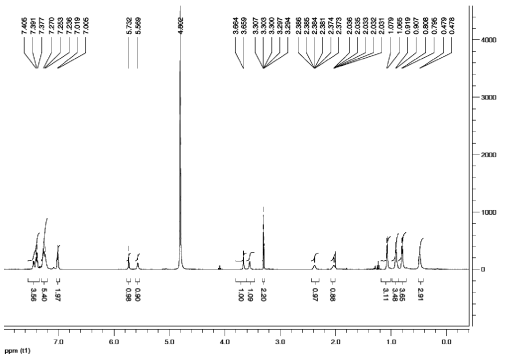
i) ligand **12** in CD_3OD



ii) ligand **12** and $Zn(OTFA)_2$ (1:0.1) in CD_3OD



iii) ligand **12** and $Zn(OTFA)_2$ (1:1) in CD_3OD



iv) ligand **2a** and $Zn(OTFA)_2$ (1:2) in CD_3OD

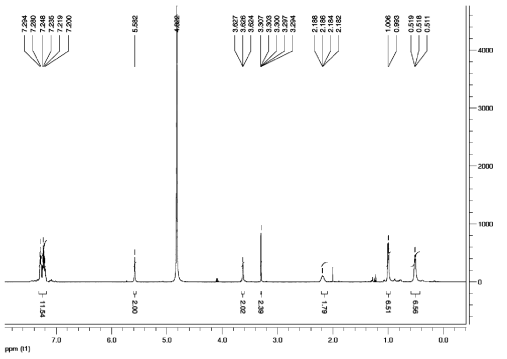
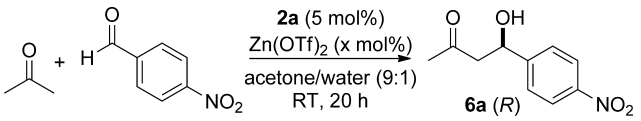


Table 7. Dependence of Aldol Reaction on 2a/Zn Ratio[a]



entry	*x* mol %	yield (%)[b]	ee (%)[c]
1	0	61	13
2	0.5	83	19
3	1	56	25
4	5	85	85
5	10	88	85

[a]Conditions: acetone (0.9 mL) and 4-nitrobenzaldehyde (0.50 mmol) and water (0.1 mL) at rt for 20 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AS-H).

enamine formation (**I**), where zinc complexation only stabilizes the formation of an enamine intermediate in water as depicted at Scheme 7, transition state **II**. Formation of the *anti*-product observed in the reaction of cyclic substrates resulted from the (*E*)-enolate of cyclohexanone (**IV**). By the same rules, aldol reaction of enamine with formaldehyde (**V**) results in formation of (*S*)-aldol.

2.7. Direct Aldol Reaction of Hydroxyacetone. Hydroxyacetone (HA) and dihydroxyacetone-based aldol reactions are of considerable importance because they provide expedient access to both natural carbohydrates and unnatural polyhydroxylated molecules of significance in medicine.[50] Most of the available knowledge on aldolases' mode of action is based on transformation of dihydroxyacetone phosphate (DHA). For a long time, the direct catalytic asymmetric aldol reaction of α-hydroxylated ketones with aldehydes had been achieved only with protein catalysts such as aldolases and catalytic antibodies.[3] Since 2000, several reports have addressed the aldol addition using both organometallic and proline catalysis.[51] Of the diastereo- and enantioselective direct aldol reactions, *anti*-selective variants have been available using proline-catalyzed reactions.[6] Recently, a number of *syn*-selective direct asymmetric aldol additions catalyzed by primary[52] and secondary[53] amines have been reported, but they are mostly limited to protected hydroxy- and dihydroxyacetones. Although some of these catalysts gave good results in organic medium,[54] they are limited to protected donors and failed to give promising results in the presence of water with unprotected hydroxyacetone.[55] In 2009, Singh presented chiral cyclohexyldiamine-based catalyst that efficiently catalyzes the *syn*-selective addition to hydroxyacetone donor in DMF/water (9:1) solution with high enantioselectivity.[56] The presented catalyst contained aromatic substituents forming a hydrophobic cavity with the reactants in aqueous medium. Thus, the catalyst successfully mimic enzymes' mode of action, and the reaction take place in this cavity, resulting in high stereoselectivity. The idea behind this design is that water-soluble substrate (i.e., natural dihydroxyacetone phosphate) can be efficiently activated in hydrophobic pockets of water-unsoluble catalyst (i.e., natural aldolases). This reverse-solubility concept is far more acceptable for water-soluble hydroxyacetone than that presented by Barbas III, who used silyl-protected ketones.[21] Apart from the more economical merits of application of unprotected hydroxyacetone, this attempt constitutes a rare example of aqueous direct aldol reaction in homogeneous solution.

To verify this hypothesis, we decided to compare the reactivity of previously prepared bisprolinamide **2a** and

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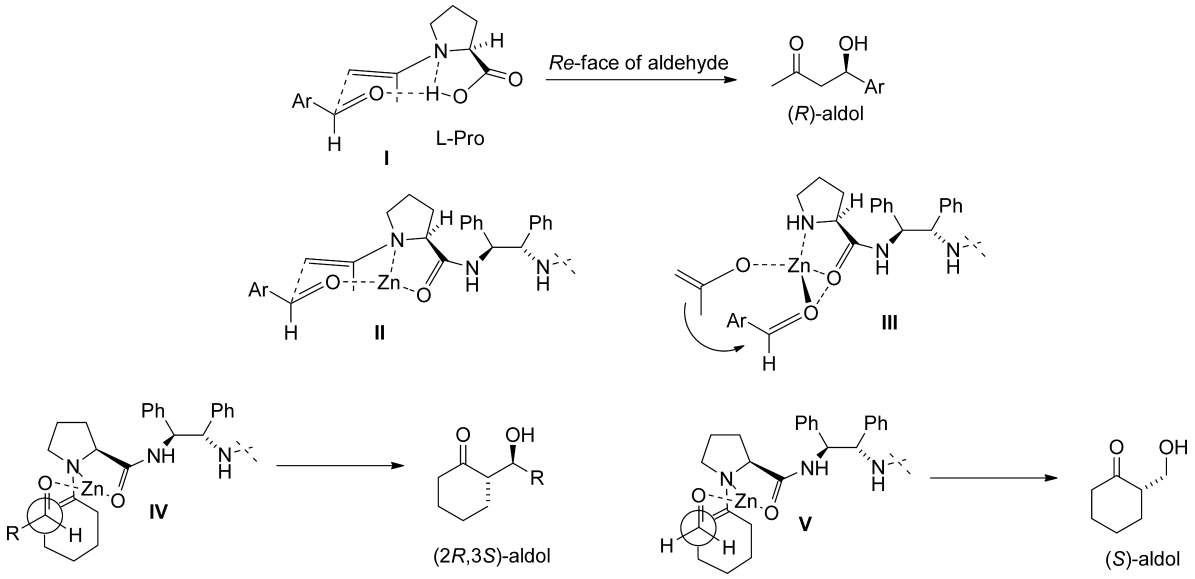
Scheme 7. Possible Structures of Transition States



bisvalinamide **12** but also to design a more hindered and lipophilic family member. We assumed that more bulky substituents can effectively protect reaction-active site and also shield one of the sites of nucleophilic attack, resulting in the higher enantioselectivity. On the other hand, recent findings suggest that selective hydrophobic acceleration can play an interesting and important part in organic synthesis in water.[57] Thus, we decided to use *O*-*tert*-butyldiphenylsilyl-protected bisserinamide **14**.

Indeed, newly designed catalyst **14** shows better reactivity when compared with **2a** and **12**. First tests have been made in organic solvents using activated 4-nitrobenzaldehyde to asses reactivity and selectivity of all three organocatalysts without additional hydrogen bond interactions. The observations collated in Table 8 revealed that the reaction of aromatic aldehyde and 5 equiv of hydroxyacetone (HA) led to *syn*-diol with good diastereoselectivity and 82% ee when THF was used as a solvent (entry 4). Interestingly, monovalinamides **15**−**17** induced worse level of enantioselectivity (entries 5−7).

Catalyst **14** is even more selective for aliphatic isobutyraldehyde, yet the isolated yield was less satisfactory (entries 10, 11). To test the substrate generality the reaction of various aldehydes with HA was studied in homogeneous aqueous solution, under optimized conditions. As shown in Table 8 (entries 10−15), aromatic aldehydes with a nitro group gave very good results with only 2 equiv of ketone. For the unreactive aromatic and aliphatic aldehydes, we kept an excess of hydroxyketone and small addition of THF to maintain a homogeneous reaction mixture. Aliphatic aldehydes, although not highly reactive, delivered aldols with excellent diastereo- and enantioselectivity at room temperature (entries 13−15). For hydroxyacetone donor additives of Lewis and Brønsted acid natures did not improved the yield or selectivity of tested catalysts.[58]

We anticipated that hydroxyacetone may give the *syn*-aldol product through an (*Z*)-enamine intermediate additionally controlled by hydrogen bond formation to hydroxyl function (Scheme 8). The stereochemistry of (3*R*,4*S*)-*syn*-configured product can be explained by transition state **VI** because of the (*Z*)-enamine reacts with Re face of aldehyde. Aldehyde substituent is always placed away from catalyst's bulky parts. Such a conclusion is in a full agreement with previously observed sense of stereochemical induction observed for the reaction of hydroxyacetone in the presence of primary amino-acid-based organocatalysts.[52]

The organocatalytic reaction of hydroxyacetone presented above took place in homogeneous aqueous solution, while the formation of enamine intermediate in water is still a subject of interesting discussion.[26] To get deeper insight into the mechanism of hydroxyacetone activation by primary amine catalyst **14**, we used ESI-MS technique. Results of the analysis of the sample containing HA and **14** (1/1) in water/methanol solution are shown in Scheme 9. The presented MS spectra confirm formation of tautomeric imine/enamine in the aqueous phase: the signal at *m*/*z* 919 matches the expected molecular weight. The isotopic pattern of this signal corresponds with the calculated pattern of the expected structure.

3. CONCLUSIONS

In summary, we have developed a new family of amino-acid-based ligands for direct aldol reactions in the presence of water. In the designed systems the Lewis base (amine) activates the ketone chelating also the Lewis acid (zinc salt). In this way, the base and the Lewis acid can activate simultaneously both donor and acceptor in the chiral environment of the backbone ligand. Such a system mimic enzymes' mode of action in their natural water environment. The presented bifunctional catalysts displayed exceptionally high reactivity in the direct asymmetric aldol reactions of cyclic/acyclic ketones and aromatic and aliphatic aldehydes. The presented family of tunable catalysts showed high reactivity in the organic phase in the presence of water, in water, or even in aqueous homogeneous solvents. Bis-prolinamide ligands with zinc can be efficient catalysts for direct activation of formaldehyde, while lipophilic bis-siloxyserinamide acts as enantioselective organocatalyst for direct aldol reaction of unprotected hydroxyacetone. We proved also that even in the presence of a large amount of water the enamine is generated and reacts with the aldehyde in the organic or water phase, affording the aldol products in high enantioselectivity. Since these Zn-complexes and organocatalysts gave good results with a variety of donors and acceptors, they are in

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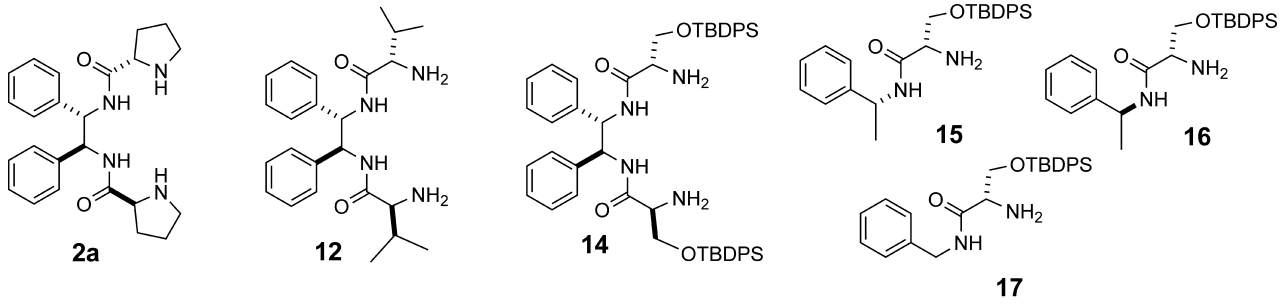
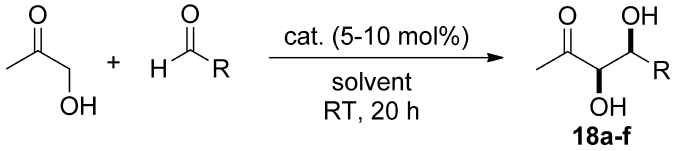
Table 8. Direct Catalytic Asymmetric Aldol Reaction in the Presence of Larger Excess of Water: Metal Complexes versus Organocatalysis

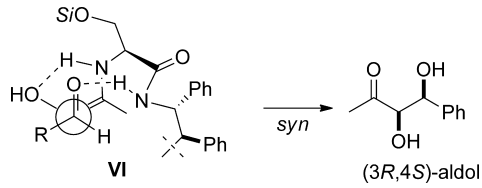




entry	RCHO	catalyst	solvent/conditions	temp (°C)	yield (%)[a]	*syn*/*anti*	ee *syn* (%)[c]
1	*p*-NO_2-C_6H_4 (**18a**)	**2a** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	72	1/1	rac
2	*p*-NO_2-C_6H_4 (**18a**)	**12** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	80	78/22	64
3	*p*-NO_2-C_6H_4 (**18a**)	**14** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	86	74/26	70
4	*p*-NO_2-C_6H_4 (**18a**)	**14** (5 mol %)	THF (1 mL), HA (5 equiv)	rt	79	8/2	82
5	*p*-NO_2-C_6H_4 (**18a**)	**15** (5 mol %)	THF (1 mL), HA (5 equiv)	rt	56	72/28	64
6	*p*-NO_2-C_6H_4 (**18a**)	**16** (5 mol %)	THF (1 mL), HA (5 equiv)	rt	58	66/34	64
7	*p*-NO_2-C_6H_4 (**18a**)	**17** (5 mol %)	THF (1 mL), HA (5 equiv)	rt	45	66/34	60
8	*i*Pr (**18b**)	**2a** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	7	28/72	70 (*anti*)
9	*i*Pr (**18b**)	**12** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	8	95/5	80
10	*i*Pr (**18b**)	**14** (5 mol %)	DCM (1 mL), HA (5 equiv)	rt	21	95/5	90
11	*i*Pr (**18b**)	**14** (5 mol %)	PhMe (1 mL), HA (5 equiv)	rt	33	95/5	92
			Reactions in the Presence of Water				
10	*p*-NO_2-C_6H_4 (**18a**)	**14** (5 mol %)	THF (0.9 mL), H_2O (0.1 mL), HA (2 equiv)	rt	95	8/2	86
11	*o*-Cl-C_6H_4 (**18c**)	**14** (10 mol %)	THF (0.1 mL), H_2O (0.1 mL), HA (0.9 mL)	rt	88	9/1	96
12	C_6H_5 (**18d**)	**14** (10 mol %)	THF (0.1 mL), H_2O (0.1 mL), HA (0.9 mL)	rt	44	75/25	82
13	*i*Pr (**18b**)	**14** (10 mol %)	THF (0.1 mL), H_2O (0.1 mL), HA (0.9 mL)	rt	59	99/1	91
14	*c*Hex (**18e**)	**14** (10 mol %)	THF (0.1 mL), H_2O (0.1 mL), HA (0.9 mL)	rt	42	99/1	99
15	Ph_2CH (**18f**)	**14** (10 mol %)	THF (0.1 mL), H_2O (0.1 mL), HA (0.9 mL)	rt	35	99/1	97

[a]Yield refers to combined yield of isolated diastereomers. Conditions: catalyst (5 mol %), aldehyde (0.50 mmol), ketone (2.5 mmol) in organic solvent (1 mL) or catalyst **14** (10 mol %), aldehyde (0.50 mmol), THF (0.9 mL), H_2O (0.1 mL), HA (0.9 mL). [b]Diastereoselectivity was determined by HPLC and ^{1}H NMR analysis of the isolated diastereomers. [c]Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H).

Scheme 8. Possible Structures of Transition States



contrast with the type II and type I aldolases that are limited to the use of selected donors only. Thus, these catalysts not only mimic but function better than aldolases.

4. EXPERIMENTAL SECTION

General Information. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer. ^{1}H NMR spectra were measured at 200 and 400 MHz in $CDCl_3$. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad), coupling constants (in Hz), and assignment. ^{13}C NMR spectra were measured at 50 and 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High resolution mass spectra (HRMS) were performed on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Optical rotations were measured on a digital polarimeter at room temperature. Reactions were controlled using TLC on silica [alu-plates (0.2 mm)]. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over anhydrous sodium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240−400 mesh). HPLC analysis were performed on HPLC system equipped with chiral stationary phase columns, detection at 254 nm.

Synthesis and spectral data for compounds **1** and **2a**−**c**,[33,35] **3**,[35] **4**, and **5**[59] were reported previously. Synthesis and NMR data of catalyst **2a** and **3**, being important for this study, are also provided below.

(1*S*,2*S*)-*N*,*N*′-Bis[(*S*)-prolyl]-1,2-diphenylethane-1,2-diamine (2a).[35] The reaction was performed under argon. Boc-L-proline (2 mmol, 430.5 mg) was dissolved in freshly distilled dichloromethane

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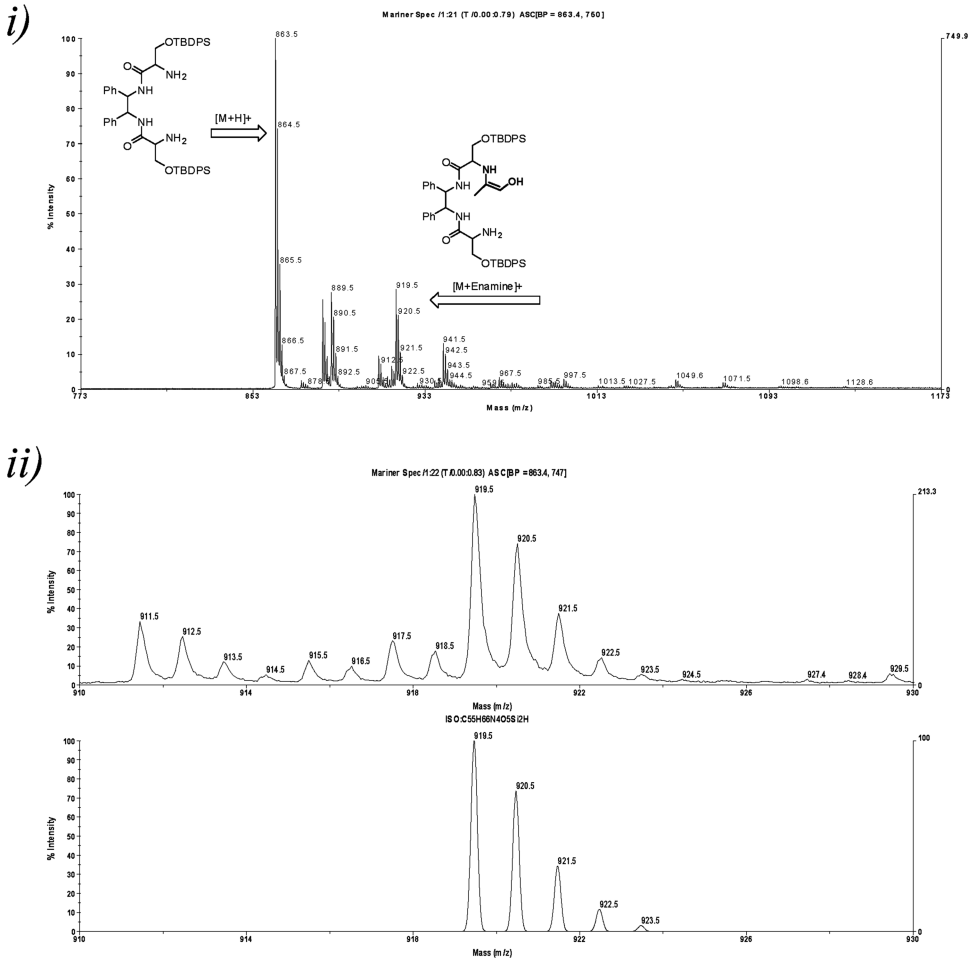
Scheme 9. (i) ESI-MS Spectra of HA and Catalyst 14 Mixture in Aqueous MeOH Solution. (ii) Measured and Calculated Isotope Pattern for Enamine Intermediate.



(5 mL). The mixture was cooled to 0 °C, and triethylamine (2.2 mmol, 222.6 mg, 307 μL) was added, followed by ethyl chloroformate (2 mmol, 217.1 mg, 191 μL). After 15 min of stirring, the precipitation of a white solid was observed and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (1 mmol, 212 mg) dissolved in dichloromethane was added. The resulting mixture was stirred at room temperature and monitored by TLC. The reaction was complete within 2 h. The reaction mixture was diluted with methyl *tert*-butyl ether and washed with saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude product (**2c**) was used for the next step without any purification. Crude (**2c**) was dissolved in dichloromethane (10 mL), and trifluoroacetic acid (1 mL) was added. The resulting mixture was stirred at room temperature and monitored by TLC (methanol/ethyl acetate = 1:2). After the consumption of starting material, a 1 M solution of NaOH was added to pH 12. The mixture was diluted with ethyl acetate, and the phases were separated. The organic phase was washed with a small volume of water and brine. It was dried over anhydrous sodium sulfate and concentrated. The crude product was submitted to column chromatography on silica gel (methanol/ethyl acetate = 1:2) to give the corresponding product with 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52−1.85 (m, 6H), 1.98−2.16 (m, 2H), 2.27 (brs, 2H), 2.78−3.03 (m, 4H), 3.67−3.74 (dd, J = 5.2, 9 Hz, 2H), 5.12−5.24 (dd, J = 2.6, 6.4 Hz, 2H), 7.03−7.21 (m, 10H), 8.46−8.49 (brd, J 6.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2, 30.8, 47.4, 58.9, 60.9, 127.6, 127.7, 128.6, 139.2, 175.3; $[\alpha]^{21}_D$ = −4.5 (*c* 1.0, CH_2Cl_2).

(1*R*,2*R*)-*N*,*N*′-Bis[(*S*)-prolyl]-1,2-diphenylethane-1,-2-diamine (3).[35] The procedure was similar to the one described for **2a** with (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine and Boc-L-proline. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62−1.89 (m, 6H), 2.06−2.19 (m, 2H), 2.24 (brs, 2H), 2.85−3.04 (m, 2H), 3.64 (dd, J = 8.8, 5 Hz, 2H), 5.20 (brs, 2H), 7.05−7.29 (m, 10H), 8.43 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2, 30.7, 47.1, 57.9, 58.0, 60.4, 127.2, 127.4, 128.2, 138.7, 175.5; $[\alpha]^{21}_D$ = −71.4 (*c* 1.0, CH_2Cl_2).

General Method for Aldol Reactions of Cyclohexanone and Acetone with Aldehydes (Table 2). Ketone (0.9 mL) and water (0.1 mL) were added to a vial containing a catalytic amount of catalyst (0.025 mmol) and zinc triflate (0.025 mmol). After vigorous stirring at room temperature for 15 min an aldehyde (0.5 mmol) was added. The resulting mixture was stirred at room temperature and monitored by TLC. The reaction mixture was poured directly on the silica gel. The aldol product (*anti*/*syn* mixture) was purified by flash column chromatography (hexane/ethyl acetate).

Spectroscopic data of **4a**−**o**[9,19,60] are in agreement with the published data.

(*S*)-2-((*R*)-2-(Benzyloxy)-1-hydroxyethyl)cyclohexanone (11).[40b] Cyclohexanone (2.7 mL) and water (0.3 mL) were added to a vial containing a catalytic amount of catalyst **2a** (0.15 mmol, 61 mg) and zinc triflate (0.15 mmol, 54.5 mg). After vigorous stirring at room temperature for 15 min, aldehyde **10** (3 mmol, 450.5 mg, 0.421 mL) was added. The resulting mixture was stirred at room temperature and monitored by TLC (hexane/ethyl acetate = 9:1). The reaction mixture was poured directly on the silica gel. The aldol product (*anti*/*syn* mixture) was purified by flash column chromatography (hexanes/ethyl acetate = 9:1) to give desired product (66%). ^{1}H NMR (300 MHz,

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$CDCl_3$) δ 1.35−2.44 (*m*, 8H), 2.64−2.76 (*m*, 1H), 3.47−3.65 (*m*, 3H), 3.88−3.98 (*m* 1H), 4.47−4.69 (*m*, 2H), 7.30−7.35 (*m*, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 27.7,30.3, 42.7, 52.5, 71,0, 71.2, 73.4, 127.6, 127.7, 128.8, 138.0, 215.0 ppm.

(1*S*,2*S*)-*N*,*N*′-Bis[(*S*)-valinyl]-1,2-diphenylethane-1,2-diamine (12). The reaction was performed under argon. Boc-L-valine (2 mmol, 455 mg) was dissolved in freshly distilled dichloromethane (5 mL). The mixture was cooled to 0 °C, and triethylamine (2.2 mmol, 222.6 mg, 307 μL) and ethyl chloroformate (2 mmol, 217.1 mg, 191 μL) were added. After 15 min of stirring, the precipitation of a white solide was observed, and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (1 mmol, 212 mg) dissolved in dichloromethane (1 mL) was added. The resulting mixture was stirred at room temperature and monitored by TLC. The reaction was complete within 2 h. The reaction mixture was diluted with dichloromethane and washed with saturated solution of sodium hydrogen carbonate and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated. The crude product was used for the next step without purification; it was dissolved in dichloromethane (10 mL), and trifluoroacetic acid (1 mL) was added. The resulting mixture was stirred at room temperature and monitored by TLC (methanol/ethyl acetate = 1:4). After reaction complition a 1 M solution of NaOH was added to pH 12. The mixture was diluted with ethyl acetate, and the aqueous phase was separated. The organic phase was washed with a small volume of water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was submitted to column chromatography on silica gel (methanol/ethyl acetate = 1:9) to give the corresponding product with 78% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 0.70 (d, J = 6.7 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H), 1.85−1.93 (m, 2H), 3.10 (d, J = 4.9 Hz, 2H), 5.38 (s, 2H), 7.18−7.23 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 20.01, 31.2, 59.1, 60.6, 127.7, 127.8, 128.6, 139.2, 175.0; IR (KBr) 3318, 2961, 1635, 1526, 700 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{24}H_{34}N_4O_2$ m/z 411.2755 ([M + H]$^+$), found m/z 411.2752 ([M + H]$^+$); $[\alpha]^{21}_D$ = −25.9, (c 0.99, CH_2Cl_2).

(*S*)-2-(Hydroxymethyl)cyclohexanone (13).[44b] Prolinamide **2a** (30.5 mg, 0.075 mmol, 10 mol %) and $Zn(OTf)_2$ (27.3 mg, 0.075 mmol, 10 mol %) were stirred for 5 min in EtOH/H_2O (9/1, 0.5 mL). To the resulting solution were added cyclohexanone (1.5 mmol, or the same amount of another ketone) and formaldehyde (0.75 mmol, 37% in water) at room temperature, and the mixture was stirred for 20 h. The mixture was extracted with CH_2Cl_2, and the combined organic layer was dried over anhydrous $MgSO_4$. The solvents were evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, = 1:1) to give desired product (55%). The reaction can be performed in 0.5 mL water instead of EtOH/water mixture, at rt for 10 h in ultrasound bath leading to aldol **13** with 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−2.10 (m, 6H), 2.22−2.52 (m, 3H), 2.56 (s, 1H), 3.50−3.60 (m, 1H), 3.62−3.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 28.2, 30.7, 42.9, 52.9, 63.5, 215.4.

(1*S*,2*S*)-*N*,*N*′-Bis[(*S*)-*tert*-butyldiphenylsiloxyserinyl]-1,2-diphenylethane-1,2-diamine (14). *N*,*N*-Dimethylformamide (1 mL) was added to a vial containing Cbz-L-serine (4.2 mmol, 1000 mg) and imidazole (10.8 mmol, 739.9 mg). The mixture was cooled to 0 °C, and *tert*-butyl(chloro)diphenylsilane (4.6 mmol, 1263.8 mg, 1196 μL) was added slowly followed by a few crystals of 4-(dimethylamino)-pyridine. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with methyl *tert*-butyl ether, and the organic phase was separated and washed with water. The aqueous phase was extracted three times with methyl *tert*-butyl ether. The combined organic phase was washed with a small volume of water and brine and then dried over anhydrous sodium sulfate and concentrated. The desired siloxyserine was purified by column chromatography (hexane/ethyl acetate = 85/15 + 1% HCOOH) and submitted to the next step (yield 97%). Reaction with amine was performed under argon. Previously obtained protected serine (4.1 mmol, 1953 mg) was dissolved in freshly distilled dichloromethane (5 mL). The mixture was cooled to 0 °C, and triethylamine (4.5 mmol, 454.6 mg, 626 μL) was added, followed by ethyl chloroformate (4.1 mmol, 443.5 mg, 390.7 μL). After 15 min of stirring, the precipitation of a white solid was observed, and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (2.0 mmol, 433 mg) dissolved in dichloromethane (1 mL) was added. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with methyl *tert*-butyl ether and washed with saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and submitted to the deprotection step. The deprotection of amino groups was performed by the hydrogenation in the presence of palladium on charcoal. The protected bis(amide) (1 equiv, ca. 2 mmol, 2.2 g) was dissolved in methanol (40 mL). Ammonia solution in methanol (0.5 equiv, 0.97 mmol, 16.52 mg, 139 μL, 7 M solution of ammonia) was added, followed by 170 mg of palladium on charcoal (moistened with water, 10% Pd basis), and the reaction was stirred overnight under hydrogen atmosphere. The mixture was filtred through a Celite plug and concentrated. The crude product was submitted to column chromatography on silica gel (dichloromethane/methanol = 95:5) to give the corresponding product with 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 18H), 1.74 (bs, 4H), 3.41−3.44 (m, 2H), 3.78−3.84 (m, 4H), 5.24 (dd, J = 6 Hz, 2H, 2.5 Hz), 7.06−7.12 (m, 10H), 7.30−7.39 (m, 10H), 7.54−7.57 (m, 10H), 8.30−8.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 26.7, 56.7, 58.7, 65.9, 127.4, 127.4, 127.6, 127.7, 128.3, 129.6, 129.7, 132.9, 133.1, 135.4, 135.5, 138.6, 172.7; IR (KBr) 3304, 2929, 2856, 1638, 1526, 1112, 700 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{25}H_{62}N_4O_4Si_2$ m/z 863.4382 ([M + H]$^+$), found m/z 863.4397 ([M + H]$^+$); $[\alpha]^{21}_D$ = +21.3, (c 0.91, MeOH).

General Method for Aldol Reactions of Hydroxyacetone with Aldehydes. Hydroxyacetone (2.5 mmol) was added to a vial containing a catalytic amount of catalyst (0.025 mmol) dissolved in tetrahydrofuran (1 mL), followed by addition of an aldehyde (0.5 mmol). The resulting mixture was stirred at room temperature and monitored by TLC. The reaction mixture was diluted with ethyl acetate and washed twice with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The pure aldol product (*syn*/*anti* mixture) was obtained by flash chromatography on a silica gel column (hexane/ethyl acetate).

Spectroscopic data of **18a**,**c**,**d**[52a,e] and **18b**,**e**,**f**[55f] are in agreement with the published data.

■ ASSOCIATED CONTENT

Supporting Information

Investigation of absolute configuration of compound **6a**; HPLC data of aldols **6**, **11**, **13**, **18**; ^{1}H and ^{13}C NMR for catalysts **2a**, **3**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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