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Highly efficient direct a larger-scale aldol reactions catalyzed by a flexible prolinamide based-metal Lewis acid bifunctional catalyst in the presence of water

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ABSTRACT

In this work, four prolinamide-based organocatalysts were readily synthesized and applied to the asymmetric direct aldol reactions of ketones and aromatic aldehydes in the presence of water. When TFA was used as an acidic additive, 10 mol % loading of **1c** afforded aldol products with good diastereoselectivity of up to 91/9 and enantioselectivity of up to 85%. When $ZnCl_2$ was added as a metal Lewis acid additive, the aldol product could be obtained with up to 99/1 *dr* and 96% *ee*. This novel prolinamide based-metal Lewis acid bifunctional organocatalyst **1c** can be efficiently used in a larger-scale reactions with the enantioselectivities being maintained at the same level, which offers a great possibility for application in industry.

1. Introduction

Enantioselective organocatalysis has provided a research avenue in which to explore the fundamental chemical parameters such as reactivity, selectivity, and mechanism and in turn leads to the discovery of many valuable reactions and catalysts [1–3]. Several efficient asymmetric methodologies for this reaction using organocatalysts have been developed, of which the most remarkable advances in the domain of proline and its derivative catalysts were made by List [4–7] and Barbas [8–11], MacMillan [12–15], Gong [16–20], Hayashi [21–24] and Xiao [25,26] et al. In the past several years, major efforts on modifying proline and chiral enamine catalysts have been focused on modification of the carboxylic acid group by introducing electronic and/or steric factors to optimize the interaction between the Brønsted acid and the aldol acceptor through hydrogen bonding [27–32]. In searching for new methodology, a lot of chiral bifunctional catalysts that tried to imitate natural enzymatic processes have been designed in asymmetric synthesis. Several examples of this sort have been reported [33–36], in which a proline/pyrrolidine molecule was mixed with a transition metal to establish the bi/multifunctional catalytic system. We utilize a prolinamide and a metal Lewis acid and develop a novel class of metal Lewis acid-enamine bifunctional catalysts with the intention to bridge more traditional transition-metal catalysis with the newly established prosperous area of organocatalysis.

The catalysts' structure can be easily tuned by introducing different metals and/or different simple chiral ligand. The combination of organocatalysis with transition-metal catalysis has emerged as a promising strategy to discover new carbon–carbon and carbon–heteroatom forming reactions.

Metal complex in the presence of water is not trivial, since most of them are decomposed under aqueous conditions. Nevertheless, a few examples of water-tolerant Lewis acids have previously been reported by Kobayashi and others [37–42]. Use of water clearly has many advantages, such as its low cost, safety, and environmentally benign nature. Several interesting reactions with unique reactivity and selectivity have been demonstrated to proceed in water or water–organic solvents [43–47], but the development of an asymmetric aqueous aldol reaction is still going on. The direct aldol systems by using the methods analogue to the actions of aldolase type II containing a zinc cofactor have still remained challenging. In fact, there were only a few reports for direct aldol reactions promoted by the metal complexes with N-donor ligands in the presence of water until now [48–50]. So a highly efficient, stereoselective, and atom economical reaction in water is currently a sought-after goal in chemistry.

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Despite the potentials of multi/bifunctional catalysts, the development of these systems is a formidable task due to the simultaneous requirements for the distance, rigidity, orientation and interactions of these functional groups. According to the mechanism of type II aldolase, four bidentate ligands tethered with chiral amines were prepared (Fig. 1). We expect that the Zn^{2+} ion may co-ordinate to ketone and can promote the formation of ketone-enolate, although the asymmetric ligand provides a chiral environment, resulting in the enantioselectivity of the current system (Fig. 2) [33–35]. In this work, compared to the traditional organocatalysts, the activity and diastereoselectivity of these catalysts were significantly enhanced for the asymmetric direct aldol reactions, and this catalyst can be used in a larger-scale reactions with the enantioselectivity being maintained at the same level, which offers a great possibility for application in industry.

2. Results and discussion

2.1. Screening of catalysts in the reaction between cyclohexanone and p-nitrobenzaldehyde

In this report we present the combination of a chiral metal complex catalyst for asymmetric aldol reactions which proceed in aqueous organic solvent. Here we present our studies toward the identification of chiral metal complexes that function as efficient aldol reaction catalysts. These ligands can be readily obtained through coupling reactions of cyclohexanediamine with amino acids. The reactions were carried out between cyclohexanone and *p*-nitrobenzaldehyde in aqueous media. As shown by Table 1, all the designed chiral prolinamide derivatives worked well in the direct aldol reactions and gave the desired β-hydroxy ketone in good yields and good enantioselectivities. Addition of $ZnCl_2$ could obviously improve the diastereoselectivities and enantioselectivities (entries 2, 4, 6, 8). Furthermore, the reaction time consumedly reduced. The best result with respect to yield and enantioselectivity was observed with prolinamide ligand **1c** and $ZnCl_2$ as additive 99% yield, 99:1 *dr* (*anti*/*syn*), and 96% *ee* (*anti*). The loading amount of $ZnCl_2$ in the reaction was also investigated. The use of 10 mol % of $ZnCl_2$ seemed to be the best for the reaction (entry 6). Although lower loading of $ZnCl_2$ slightly decreased in both yields and selectivities (entry 11), no improvement was detected when more than 5 mol % $ZnCl_2$ was used (entries 9, 10).

2.2. Effects of catalyst loading, solvents and various metal salts on the organocatalyzed direct aldol reaction

In our case, the prolinamide ligand **1c** could activate the ketone via an enamine intermediate and at the same time interact with various metal salts to activate the aldehyde for 2–4 h at room

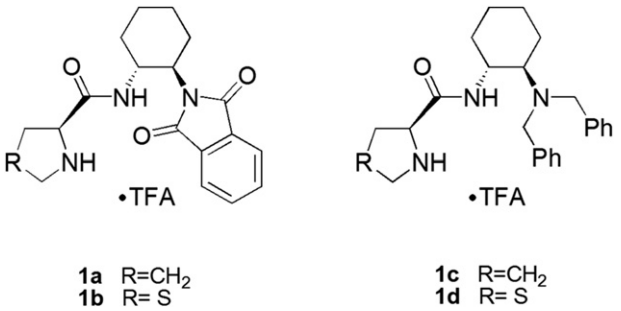


Fig. 1. Structure of the prolinamide-based ligand **1** used in this study.

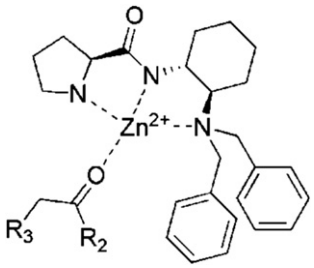
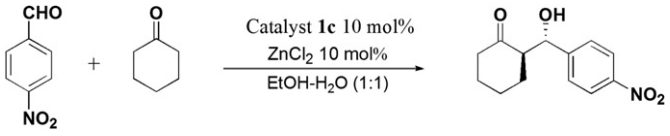


Fig. 2. Proposed transition state.

temperature. All the bifunctional catalysts showed activities. $Zn(OTf)_2$ and $HgCl_2$ displayed high activities in terms of *dr* and reaction time. However, the enantioselectivities were modest (90 and 92% *ee*; Table 2, entries 2, 6). Counteranions of the metal salts also played a role in determining the yield and enantioselectivity. Whereas $CuCl_2$ and CuCl gave reasonable *ee* values of 92 and 93% in modest yield, these results strongly suggest that metals participate in the reactions. The effect of catalyst loading on the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using ligand **1c**/$ZnCl_2$ was examined (Table 2, entries 1, 11, 12, 13). The use of 10 mol % of **1c** seemed to be the best for the reaction (entry 1).

Reactions in which water is used as the solvent are another important issue and the development of enantioselective reactions in aqueous media is a partner [51,52]. To prove the principle, the bifunctional catalysts were prepared by stirring ligand **1c** with metal salts in a molar ratio of 1:1 in corresponding solvent(s) extensively investigated topic. In this regard, direct aldol reactions in the presence of water seem to be a challenging issue which needs to be intensively explored. From Table 2, the use of an EtOH–H_2O solution instead of THF–H_2O and DMSO–H_2O mixtures improved the reaction further (Table 2, entries 1, 9, 10), and finally, at higher concentration and still at room temperature, the reaction proceeded in higher yield and with high selectivity. We also review the ratio of EtOH and water (entries 1, 7, 8, 14, 15), the best result was observed when the ratio of ethanol to water was 1:1 (1 mL), and

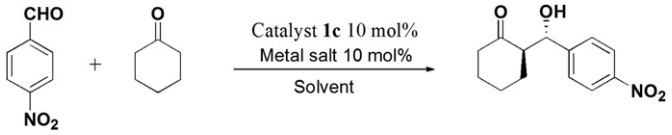
Table 1
Screening of catalysts in the reaction between cyclohexanone and *p*-nitrobenzaldehyde.[a]



Entry	Cat.	$ZnCl_2$ (mol%)	Time	Yield[b] [%]	*anti*:*syn*[c] [%]	*ee*[d] [%]
1	**1a**	0	36	90	89:11	76
2	**1a**	10	24	97	99:1	86
3	**1b**	0	36	85	86:14	69
4	**1b**	10	24	95	90:10	85
5	**1c**	0	36	92	91:9	85
6	**1c**	10	24	99	99:1	96
7	**1d**	0	36	91	96:4	74
8	**1d**	10	24	95	99:1	92
9	**1c**	20	7	99	90:10	79
10	**1c**	15	12	99	92:8	93
11	**1c**	5	36	90	94:6	94

[a] The reaction was performed with *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (4 equiv.), catalyst (10 mol %), $ZnCl_2$ (10 mol %) in the EtOH–H_2O (1:1, 1.0 mL) at room temperature.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral ^1H NMR analysis, major product is *anti*.
[d] Determined by chiral HPLC analysis of the *anti*-product.

Table 2
The direct catalytic asymmetric aldol reaction in the presence of water catalyzed by prolinamide **1c** (10 mol %) with various additives, metal salt, solvent.[a]



Entry	Metal	Solvent	Time	Yield[e][%]	*anti:syn*[f] [%]	*ee*[g][%]
1	$ZnCl_2$	EtOH–H_2O	24	99	99:1	96
2	$Zn(OTf)_2$	EtOH–H_2O	24	95	99:1	90
3	$CuCl_2·2H_2O$	EtOH–H_2O	36	90	91:9	92
4	CuCl	EtOH–H_2O	36	92	90:10	93
5	$FeCl_3·6H_2O$	EtOH–H_2O	24	95	93:7	88
6	$HgCl_2$	EtOH–H_2O	24	97	95:5	92
7	$ZnCl_2$	H_2O	5	99	87:13	85
8	$ZnCl_2$	EtOH	5	99	85:15	87
9	$ZnCl_2$	THF–H_2O	12	95	91:9	90
10	$ZnCl_2$	DMSO–H_2O	24	95	93:7	91
11[b]	$ZnCl_2$	EtOH–H_2O	10	99	90:10	90
12[c]	$ZnCl_2$	EtOH–H_2O	20	99	92:8	92
13[d]	$ZnCl_2$	EtOH–H_2O	36	90	95:5	94
14[h]	$ZnCl_2$	EtOH–H_2O	20	97	91:9	82
15[i]	$ZnCl_2$	EtOH–H_2O	20	95	92:8	75

[a] The reaction was performed with *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (4 equiv.), catalyst **1c** (10 mol %), metal salt (10 mol %) in the solvent (1.0 mL) at room temperature.
[b] 20 mol % **1c** was additive.
[c] 15 mol % **1c** was additive.
[d] 5 mol % **1c** was additive.
[e] Isolated yield after chromatography on silica gel.
[f] Determined by chiral ^1H NMR analysis.
[g] Determined by chiral HPLC analysis of the *anti*-product.
[h] $V_{EtOH}/V_{H2O} = 5:1$.
[i] $V_{EtOH}/V_{H2O} = 1:5$.

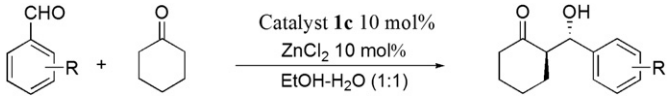
99% chemical yield and 96% *ee* value were obtained. As expected, when EtOH or H_2O were used alone as the solvent, the results is not satisfactory (entries 7, 8).

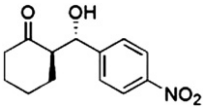
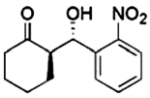
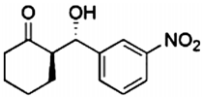
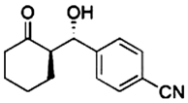
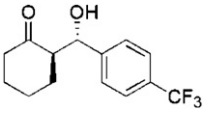
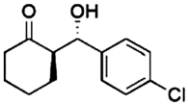
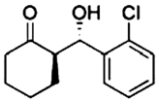
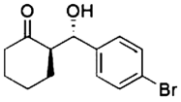
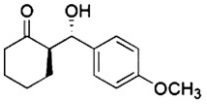
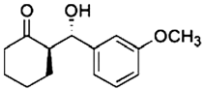
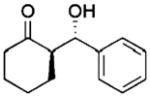
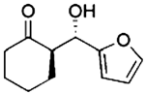
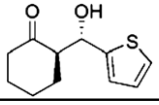
2.3. The asymmetric aldol reactions of ketone with various aryl aldehydes in the presence of water

To test the substrate generality of this organocatalyzed direct aldol reaction, the reactions of various aromatic aldehydes with cyclohexanone were studied under the optimized conditions. The results are summarized in Table 3. It can be seen that a wide range of aromatic aldehydes can effectively participate in the aldol reaction, and aldol adducts 2–14 derived from their corresponding aromatic aldehydes and cyclohexanone could be accessed. In the presence of 10 mol % catalyst **1c** and $ZnCl_2$ (10 mol %), most reactions between cyclohexanone and various aromatic aldehydes afforded the aldol products in excellent yields and perfect *ee* values. In general, the reaction between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products in excellent yields (80–99%) enantioselectivities (85–99% *ee* for *anti*-isomer) and excellent diastereoselectivities (*anti*/*syn* 80:20 to 99:1; Table 3, entries 1–13).

The feasibility of using other cyclic and acyclic ketones as aldol donors was then examined. As showed in Table 4, when 4-methylclohexanone was used as an aldol donor, a good *dr* of 98:2 with excellent *ee* 96% for the antisomer were received. We also examined the feasibility of using acyclic ketones, such as hydroxyacetone, acetone et al. as aldol donors. Although a longer reaction time was required in comparison with cyclic ketones, satisfactory results were obtained. The proline derivative organocatalyst **1c**

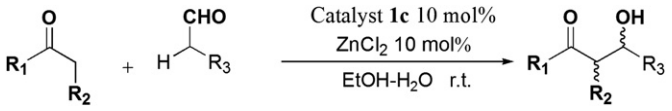
Table 3
The asymmetric aldol reactions of cyclohexanone with various aryl aldehydes in the presence of water.[a]

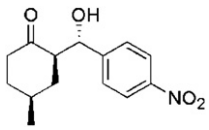
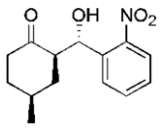
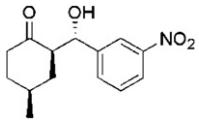
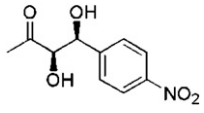
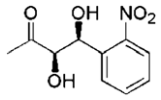
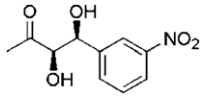
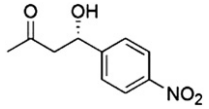
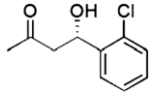
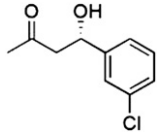
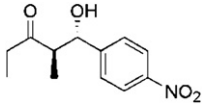


Entry	Product	No.	Yield[b] [%]	*anti:syn*[c] [%]	*ee*[d] [%]
1		2	99	93:7	96
2		3	97	94:6	87
3		4	90	91:9	91
4		5	95	99:1	99
5		6	93	99:1	99
6		7	90	90:10	93
7		8	92	96:4	94
8		9	95	95:5	85
9		10	85	82:18	90
10		11	83	93:7	96
11		12	80	90:10	87
12		13	90	93:7	92
13		14	92	92:8	90

[a] The reaction was performed with *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (4 equiv.), catalyst **1c** (10 mol %), metal salt (10 mol %) in the solvent (1.0 mL) at room temperature.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral ^1H NMR analysis.
[d] Determined by chiral HPLC analysis of the *anti*-product.

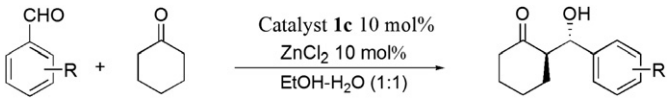
Table 4
Direct asymmetric aldol reactions between ketones and aromatic aldehydes in the presence of water, catalyzed by **1c**.[a]

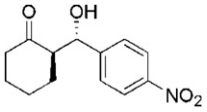
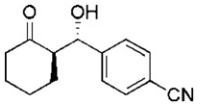
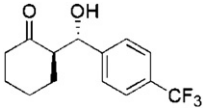
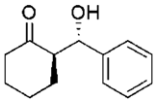


Entry	Product	No.	Time	Yield[b][%]	*anti*:*syn*[c][%]	*ee*[d][%]
1		15	24	95	90:10	96
2		16	24	92	92:8	95
3		17	24	97	98:2	92
4		18	36	90	8:92	95
5		19	36	92	11:89	96
6		20	36	97	18:82	>99
7		21	36	92	–	79
8		22	36	90	–	95
9		23	36	87	–	93
10		24	36	94	80:20	85

[a] The reaction was performed with aldehyde (0.25 mmol), ketone (4 equiv.), catalyst **1c** (10 mol %), $ZnCl_2$ (10 mol %) in the EtOH–H_2O (1:1, 1.0 mL) at room temperature.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral ^1H NMR analysis.
[d] Determined by chiral HPLC analysis of the *anti*-product.

Table 5
Large-scale asymmetric aldol reactions.[a]



Entry	Product	Time	Yield[b] [%]	*anti*:*syn*[c] [%]	*ee*[d] [%]
1		24	95	98:2	96
2		24	93	97:3	99
3		24	92	98:2	99
4		24	87	90:10	87

[a] The reaction was performed with aldehyde (20 mmol), ketone (4 equiv.), catalyst **1c** (10 mol %), $ZnCl_2$ (10 mol %) in the EtOH–H_2O (1:1, 80 mL) at room temperature.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^1H NMR analysis, major product is *anti*.
[d] Determined by HPLC analysis of the *anti*-product.

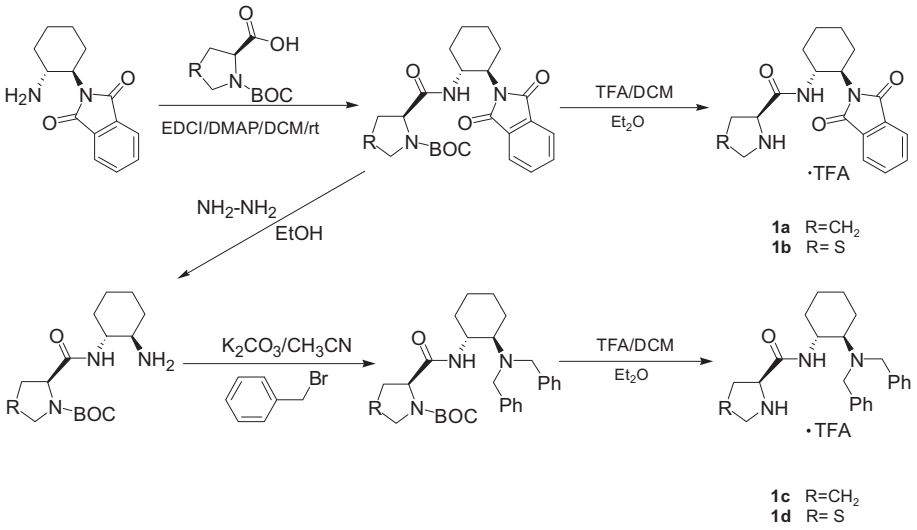
catalyzed direct aldol reactions of hydroxyacetone and acetone et al. (Table 4, entries 4–10) and the aldol products were obtained in high yields (up to 97%) with excellent enantioselectivities (up to 99% *ee*).

2.4. The screen of a larger-scale reactions between cyclohexanone and aryl aldehydes

A larger-scale asymmetric aldol reactions were then performed with 20 mmol of aromatic aldehydes and 4 equiv. of ketones. The same catalyst loading of 10 mol % as used in the experimental scale was used. The larger-scale experiments proceeded smoothly using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 5, the enantioselectivities were maintained at the same level for the larger-scale reactions which offers great possibilities for applications in industry.

3. Conclusion

In summary, a series of chiral prolinamides based on cyclohexanediamine were designed and were successfully used as chiral ligands in metal-assisted asymmetric direct aldol reactions in aqueous media. This catalytic direct aldol provides an easy access to the chiral β-hydroxy ketones with good diastereoselectivities (*dr* up to 99:1) and high enantioselectivities (up to 99% *ee*). The catalysts' structure can be easily tuned by introducing different metals and/or different chiral prolinamides. The present study reveals an interesting area of aqueous asymmetric aldol reactions between application of metal salt and organocatalysis. This novel prolinamide based-metal Lewis acid bifunctional organocatalyst **1c** can be



Scheme 1. Synthesis of catalysts **1a**–**1d**.

efficiently used in a larger-scale reactions with the enantioselectivities being maintained at the same level, which offers a great possibility for application in industry.

4. Experimental

4.1. General information

The starting reagents used during the course of preparing prolinamide ligands **1a**–**1d** were purchased from the Aldrich Company. All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) and/or ninhydrin both in ethanol stain. THF was freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere immediately prior to use, CH_2Cl_2 was distilled after drying over anhydrous CaH_2 and stored over 4 Å molecular sieves. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (d) are given in ppm relative to TMS as the internal reference, coupling constants (*J*) in Hz. IR spectra were recorded on a spectrometer. Melting points were measured on a digital melting point apparatus. Mass spectra (MS) were measured with a spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak AD-H (4.6 mm × 250 mm), Chiralcel OD-H (4.6 mm × 250 mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at $\lambda = 589$ nm.

4.2. The general procedure of aldol reactions

A mixture of catalyst (0.025 mmol), metal salt (0.025 mmol), ketone (1 mmol) contained in 1.0 mL of EtOH–H_2O (1:1) was stirred at room temperature for 2 h. Subsequently, the aldehyde (0.25 mmol) was introduced. The reaction mixture was stirred at room temperature until the reaction was judged to be complete based on TLC analysis. The reaction was quenched by adding saturated NH_4Cl solution, and the organic material was extracted with ethyl acetate (2 × 20 mL). The combined organic extract was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography to give the pure aldol adduct.

The crude product before SiO_2 chromatography was submitted to ^1H NMR analysis to determine diastereomeric ratio. The product after SiO_2 chromatography was analyzed by HPLC to determine the enantiomeric as well as the diastereomeric ratios; the latter matched, within allowable limits, the values determined by ^1H NMR analysis. The *syn* and *anti* diastereomers of the aldols were readily distinguished in ^1H NMR spectroscopy by the diagnostic chemical shifts of –CHOH– proton, cf. SI for the chemical shift data. The characterization data of all the aldol reaction products has been reported by the literature [31–33,46–50], and the detailed characterization data can be seen by the supplementary material.

4.3. General procedure for the preparation of catalysts ***1a*–*1d***

4.3.1. Typical procedure for the synthesis of ***1a*/*1b*** *[49]*

Compound **1a** is referred to as an example: all prolinamides were synthesized starting from (1*R*,2*R*)-*N*-phthaloyl-1,2-diaminocyclohexane, under a dry Ar atmosphere, to a stirred solution of *N*-Boc-L-proline (215 mg, 1 mmol, 1 equiv), DMAP (42 mg, 0.3 equiv), EDCI (244 mg, 1.1 equiv), and amine (235 mg, 0.8 equiv) were dissolved in dichloromethane (10 mL). The resulting mixture was stirred at room temperature for 2 days. Then the mixture was concentrated to half of the volume in vacuo and the resulting mixture was partitioned between EtOAc (100 mL) and 0.5 M aqueous HCl (50 mL). The organic layer was washed with half-saturated brine (25 mL), dried (Na_2SO_4), filtered, and concentrated followed by flash column chromatography (AcOEt/petroleum ether = 1:4) to give *N*-Boc-L-prolinamide. To a stirred solution of *N*-Boc-L-prolinamide (442 mg, 1 mmol) in dichloromethane (10 mL), TFA (4.0 mL) was added and stirred at room temperature for 12 h. After evaporation of the solvent, the resulting residue was deluted with Et_2O and recrystallized, obtained pure product **1a** as an off-white solid. (Scheme 1)

4.3.2. Typical procedure for the synthesis of ***1c*/*1d*** *[49]*

Compound **1c** is referred to as an example: A solution of (*S*)-tert-butyl-2-((1*R*, 2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamoyl) pyrrolidine-1-carboxylate (0.44 g, 1 mmol) in 10 mL ethanol was refluxed with hydrazine monohydrate (0.2 mL) for 5 h. The reaction mixture was then cooled to room temperature and diethyl ether was

added to it to precipitate phthaloyl hydrazide completely. The white solid was filtered and the filtrate was evaporated to afford (*S*)-tert-butyl-2-((1*R*, 2*R*)-2-aminocyclohexylcarbamoyl)pyrrolidine-1-carboxylate as light yellow solid. This was used in the following step without further purification. To a solution of (*S*)-tert-butyl-2-((1*R*, 2*R*)-2-aminocyclohexylcarbamoyl)pyrrolidine-1-carboxylate (0.244 g, 1 mmol) in 20 mL abs. CH_3CN and K_2CO_3 (0.32 g, 2.3 mmol) was added benzyl bromide (0.3 mL, 2.5 mmol) and the resulting mixture was heated to reflux for 24 h. The reaction mixture was cooled to ambient temperature and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (20 mL) and water (20 mL); the organic layer was separated and the aqueous layer (pH ~10) was extracted with dichloromethane (3 × 15 mL). The combined organic layer was dried over anh. Na_2SO_4 and the solvent was removed in vacuo to obtain pure production as an off-white crystalline solid. To a stirred solution of *N*-Boc-L-prolinamide (491 mg, 1 mmol) in dichloromethane (10 mL), TFA (4.0 mL) was added and stirred at room temperature for 12 h. After evaporation of the solvent, the resulting residue was diluted with Et_2O and recrystallized, obtained pure product **1c** as an off-white solid.

*4.3.2.1. (S)-N-((1R,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyrrolidine-2-carboxamide(**1a**).* White solid. Yield: 90%; $[\alpha]_D^{20} = -44.4$ (c = 0.33, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3327.01, 3292.64, 2934.35, 1766.21, 1709.90, 1663.27, 1466.95, 1450.19, 719.05 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (ppm) δ = 1.25–1.56 (m, 6H), 1.71–2.06 (m, 7H), 2.49–2.63 (m, 1H), 2.73–2.76 (m, 1H), 2.83–2.89 (m, 1H), 3.49–3.54 (dd, J = 9.4, 4.9 Hz, 1H), 3.91–3.97 (td, J = 12.3, 3.7 Hz, 1H), 4.39–4.51 (qd, J = 11.2, 4.3 Hz, 1H), 7.51–7.53 (d, 1H), 7.66–7.68 (m, 2H), 7.79–7.82 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) (ppm) δ = 24.58, 25.41, 25.73, 28.51, 30.46, 32.92, 47.02, 48.62, 54.97, 60.08, 122.92, 131.9, 133.72, 168.42, 174.62; HRMS (ESI): calcd. for $(C_{19}H_{23}N_3O_3)^+$ 341.1718, found 341.1719.

*4.3.2.2. (R)-N-((1R,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)thiazolidine-4-carboxamide(**1b**).* White solid. Yield: 92%; $[\alpha]_D^{20} = -51.3$ (c = 0.33, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3335.07, 3298.67, 2964.22, 1773.23, 1711.60, 1668.25, 1458.45, 1435.26, 720.08 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) (ppm) δ = 1.18–1.39 (m, 3H), 1.44–1.57 (m, 1H) 1.80–1.91 (m, 3H), 2.05–2.09 (d, 1H), 2.54–2.59 (m 1H), 2.75–2.82 (m, 2H), 3.72–3.75 (d 1H), 3.92–4.0 (m 2H), 4.07–4.10 (d 1m), 4.43–4.55 (qd J = 10.2, 4.4, 1H), 6.97–7.0 (d 1H), 7.66–7.69 (m 2H), 7.80–7.83 (m 2H); ^{13}C NMR(75 MHz, $CDCl_3$) (ppm) δ = 24.53, 25.34, 28.44, 32.81, 33.07, 49.21, 53.14, 54.85, 63.64, 123.12, 133.76, 170.25; HRMS (ESI) : calcd. for $(C_{18}H_{21}N_3O_3S)^+$ 359.1335, found 359.1337.

*4.3.2.3. (S)-N-((1R,2R)-2-(dibenzylamino)cyclohexyl)pyrrolidine-2-carboxamide (**1c**).* Light yellow solid. Yield: 75%; $[\alpha]_D^{20} = 6.0$ (c = 0.33, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3340.69, 2926.94, 2855.59, 1650.32, 1512.42, 1498.89, 1451.35, 752.30, 701.25 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) (ppm) δ = 0.79–0.90 (m, 1H), 1.03–1.16 (m, 1H), 1.23–1.38 (m, 2H), 1.59–1.63 (d, 1H), 1.80–2.03 (m, 4H), 2.09–2.28 (m, 3H), 2.35–2.45 (m, 2H), 3.16–3.20 (m, 2H), 3.35–3.39 (d, 2H), 3.69–3.82 (m, 4H), 7.22–7.35 (m, 10H); ^{13}C NMR(75 MHz, $CDCl_3$) (ppm) δ = 23.17, 24.66, 25.48, 26.36, 30.30, 32.70, 47.36, 49.95, 33.25, 60.24, 60.85, 126.84, 128.11, 128.89, 140.13, 174.50; HRMS (ESI): calcd. for $(C_{25}H_{33}N_3O)^+$ 391.2654, found 391.2657.

*4.3.2.4. (R)-N-((1R,2R)-2-(dibenzylamino)cyclohexyl)thiazolidine-4-carboxamide (**1d**).* Light yellow solid. Yield: 70%; $[\alpha]_D^{20} = 3.3$ (c = 0.33, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3322.44, 2926.58, 1647.70, 1564.28, 1492.76, 1449.95, 1109.28, 732.67, 700.86 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) (ppm) δ = 0.84–0.95 (m, 1H), 1.04–1.16 (m, 1H), 1.17–1.41 (m, 3H), 1.62–1.66 (d 1H), 1.80–1.86 (d, 2H), 2.11–2.15 (d, 1H), 2.37–2.41 (d, 2H), 3.16–3.22 (m, 1H), 3.32–3.39 (m, 3H), 3.75–3.85 (m 3H), 3.98–4.02 (t, 1H), 4.16–4.28 (m, 2H), 7.25–7.35 (m, 10H); ^{13}C NMR(75 MHz, $CDCl_3$) (ppm) δ = 22.98, 24.62, 25.40, 32.59, 35.56, 50.14, 53.35, 54.10, 60.52, 66.52, 127.05, 128.27, 129.13, 139.74, 170.34; HRMS (ESI): calcd. for $(C_{24}H_{31}N_3OS)^+$ 409.2235, found 409.2238.

4.3.2.5. (2R,10S)-2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexan-1-one 2 [47,53]. Yield 99%, (*anti*/*syn*) = 99:1, *ee* = 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 20:80; flow rate 0.5 mL/min, 25 °C, λ = 254 nm; t_R = 43.3 min (*anti*, major), t_R = 34.0 min (*anti*, minor)). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, 2H, J = 8.7 Hz), 7.51 (d, 2H, J = 8.7 Hz), 4.90 (dd, 1H, J = 8.4, 3.0 Hz), 4.09 (d, 1H, J = 3.0 Hz), 2.65–2.45 (m, 2H), 2.36 (td, 1H, J = 13.2, 5.7 Hz), 2.17–2.06 (m, 1H), 1.87–1.78 (m, 1H), 1.67–1.51 (m, 3H), 1.45–1.31 (m, 1H).

4.3.2.6. (2R,10S)-2-(Hydroxy-(2-nitrophenyl)methyl)cyclohexan-1-one 3 [47,53]. Yield: 97%; (*anti*/*syn*) = 94:6, *ee* = 87%. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 95/5), 25 °C, 254 nm, 0.5 mL/min; major anti enantiomer t_R = 41.9 min and minor enantiomer t_R = 50.7 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 5.45 (d, J = 6.6 Hz, 1H), 3.90 (br, 1H), 2.82–2.70 (m, 1H), 2.50–2.40 (m, 1H), 2.34 (td, J = 12.3 Hz and J = 5.7 Hz, 1H), 2.15–2.06 (m, 1H), 1.90–1.55 (m, 4H).

4.3.2.7. (2R,10S)-2-(Hydroxy-(3-nitrophenyl)methyl)cyclohexan-1-one 4 [47,53]. Yield: 90%; (*anti*/*syn*) = 91:9, *ee* = 91%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80/20), 25 °C, 254 nm, 0.5 mL/min; major anti enantiomer t_R = 41.9 min and minor anti enomer t_R = 32.3 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21(d, J = 8.7 Hz, 2H), 7.51(d, J = 8.7 Hz, 2H), 4.90(dd, J = 8.4 Hz and J = 3.0 Hz, 1H), 4.09(d, J = 3.0 Hz, 1H), 2.65–2.45 (m, 2H), 2.36 (td, J = 13.2 Hz and J = 5.7 Hz, 1H), 2.17–2.06 (m, 1H), 1.87–1.78 (m, 1H), 1.67–1.51 (m, 3H), 1.45–1.31 (m, 1H).

4.3.2.8. (2R,10S)-2-(Hydroxy-(4-cyanophenyl)methyl)cyclohexan-1-one 5 [47,53]. Yield: 95%; (*anti*/*syn*) = 99:1, *ee* = 99%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80/20), 25 °C, 254 nm, 0.5 mL/min; major anti enantiomer t_R = 22.5 min and minor enantiomer t_R = 18.0 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 4.85 (dd, J = 8.1 Hz and J = 3.0 Hz, 1H), 4.11 (d, J = 3.0 Hz, 1H), 2.65–2.44 (m, 2H), 2.37 (td, J = 12.9 Hz and J = 6.0 Hz, 1H), 2.17–2.06 (m, 1H), 1.88–1.77 (m, 1H), 1.72–1.47 (m, 3H), 1.44–1.31 (m, 1H).

4.3.2.9. (2R,10S)-2-(Hydroxy-(4-(trifluoromethyl)phenyl)methyl) cyclohexan-1-one 6 [47,53]. Yield: 99%; (*anti*/*syn*) = 99:1, *ee* = 99%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 25 °C, 254 nm, 0.5 mL/min; major anti enantiomer t_R = 34.3 min and minor enantiomer t_R = 26.9 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.55 (m, 3H), 7.40 (t, J = 7.2 Hz, 1H), 5.30 (d, J = 9.3 Hz, 1H), 4.03 (t, J = 3.0 Hz, 1H), 2.81–2.69 (m, 1H), 2.55–2.45 (m, 1H), 2.37 (td, J = 12.9 Hz and J = 4.8 Hz, 1H), 2.15–2.03 (m, 1H), 1.81–149 (m, 3H), 1.48–1.23 (m, 1H).

4.3.2.10. (2R,10S)-2-(Hydroxy-(4-chlorophenyl)methyl)cyclohexan-1-one 7 [47,53]. Yield: 90%; (*anti*/*syn*) = 90:10, *ee* = 93%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 25 °C, 220 nm, 0.5 mL/min;

major anti enantiomer t_R = 39.2 min and minor enantiomer t_R = 33.2 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (dd, J = 20.4 Hz and J = 8.4 Hz, 4H), 4.76 (dd, J = 8.7 Hz and J = 2.7 Hz, 1H), 3.99 (d, J = 3.0 Hz, 1H), 2.61–2.44 (m, 2H), 2.35 (td, J = 12.9 Hz and J = 5.4 Hz, 1H), 2.15–2.05 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.50 (m, 3H), 1.37–1.20 (m, 1H).

4.3.2.11. (2R,10S)-2-(Hydroxyl-(2-chlorophenyl)methyl)cyclohexan-1-one 8 [47,53]. Yield: 92%; (*anti*/*syn*) = 96:4, *ee* = 94%. Enantiomeric excess was determined by HPLC with Chiralcel OD-H (hexane/*i*-PrOH = 95/5), 25 °C, 220 nm, flow rate 1.0 mL/min, major anti enantiomer t_R = 9.7 min and minor anti enantiomer t_R = 12.3 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.4 Hz, 1H), 7.20–7.34 (m, 3H), 5.35 (d, J = 8.0 Hz, 1H), 3.88 (s, 1H), 2.65–2.71 (m, 1H), 2.46–2.49 (m, 1H), 2.31–2.39 (m, 1H), 2.05–2.13 (m, 1H), 1.53–1.84 (m, 5H).

4.3.2.12. (2R,10S)-2-(Hydroxy-(4-bromophenyl)methyl)cyclohexan-1-one 9 [47,53]. Yield: 95%; (*anti*/*syn*) = 95:5, *ee* = 85%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 25 °C, 220 nm, 0.8 mL/min; major anti enantiomer t_R = 27.0 min and minor anti enantiomer t_R = 22.4 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 4.75 (dd, J = 8.7 Hz and J = 2.7 Hz, 1H), 3.99 (d, J = 3.0 Hz, 1H), 2.61–2.44 (m, 2H), 2.35 (td, J = 12.9 Hz and J = 6.3 Hz, 1H), 2.15–2.04 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.50 (m, 3H), 1.37–1.20 (m, 1H).

4.3.2.13. (2R,10S)-2-[Hydroxy-(4-methoxy-phenyl)methyl]cyclohexan-1-one 10 [47,53]. Yield: 85%; (*anti*/*syn*) = 82:18, enantiomeric excess: 90% (anti-diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.8 mL/min, 25 °C, λ = 221 nm) t_R = 32.5 min (anti, major) and t_R = 30.8 min (*anti*, minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.76 (d, J = 7.6 Hz, 1H), 3.94 (s, 1H), 3.83 (s, 3H), 2.34–2.65 (m, 3H), 2.08–2.14 (m, 1H), 1.55–1.82 (m, 6H), 1.20–1.40 (m, 2H) ppm.

4.3.2.14. (2R,10S)-2-(Hydroxy-(3-methoxy-phenyl)-methy-l)cyclohexan-1-one 11 [47,53]. Yield: 83%; (*anti*/*syn*) = 93:7, *ee* = 96%. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 25 °C, 220 nm, 0.5 mL/min; major anti enantiomer t_R = 56.3 min and minor enantiomer t_R = 51.1 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.33 (m, 1H), 6.80–7.00 (m, 3H), 4.75–4.85 (d, J = 8.7 Hz, 1H), 3.85 (s, 3H), 2.30–2.75 (m, 3H), 2.00–2.15 (m, 1H), 1.55–1.90 (m, 4H), 1.20–1.40 (m, 1H).

4.3.2.15. (2R,10S)-2-(Hydroxy-(phenyl)-methyl)cyclohexan-1-one 12 [47,53]. Yield: 80%; (*anti*/*syn*) = 90:10, *ee* = 87%. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 90/10), 25 °C, 220 nm, 0.5 mL/min; major anti enantiomer t_R = 19.6 min and minor enantiomer t_R = 30.6 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.24 (m, 5H), 4.80 (d, J = 9.0 Hz, 1H), 4.00 (m, 1H), 2.70–2.56 (m, 1H), 2.55–2.44 (m, 1H), 2.34 (td, J = 12.3, 5.4 Hz, 1H), 2.16–2.03 (m, 1H), 1.87–1.73 (m, 1H), 1.72–1.50 (m, 3H), 1.40–1.22 (m, 1H).

4.3.2.16. (R)-2-((S)-Furan-2-yl(hydroxy)methyl)cyclohexanone 13 [47]. *ee* and *dr* was determined by HPLC analysis(Chiralpak AD-H, Hexane: *i*-PrOH = 95:5, 0.5 mL/min, 254 nm; t_R (minor) = 47.143min, t_R (major) = 54.962min).

4.3.2.17. (R)-2–((S)-hydroxy(thiophen-2-yl)methyl)cyclohexanone 14 [47]. *ee* and *dr* was determined by HPLC analysis (Chiralpak AD-H, Hexane:*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t_R (minor) = 16.609min, t_R (major) = 14.857 min).

4.3.2.18. (2R,10S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)-4-methyl-cyclohexan-1-one 15 [47,53]. Yield 95%, (*anti*/*syn*) = 90:10, enantiomeric excess: 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 25 °C, λ = 254 nm; t_R = 41.3 min (*anti*, minor), t_R = 36.3 min (*anti*, major)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–8.23 (m, 2H), 7.47–7.52 (m, 2H), 4.92 (d, J = 8.6 Hz, 1H), 3.82 (br, 1H), 2.72–2.78 (m, 1H), 2.48–2.50 (m, 1H), 2.36–2.43 (m, 1H), 2.07–2.09 (m, 1H), 1.89–1.93 (m, 1H), 1.78–1.81 (m, 1H), 1.54–1.60 (m, 1H), 1.33 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H).

4.3.2.19. (2R,10S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-4-methyl-cyclohexan-1-one 16 [47,53]. Yield 92%, (*anti*/*syn*) = 92:8, enantiomeric excess: 95% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.8 mL/min, 25 °C, λ = 254 nm; t_R = 34.7 min (*anti*, minor), t_R = 32.5 min (*anti*, major)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.84 (m, 1H), 7.72–7.74 (m, 1H), 7.62 (m, 1H), 7.40–7.45 (m, 1H), 5.42 (d, J = 7.2 Hz, 1H), 3.95 (br, 1H), 2.89–2.92 (m, 1H), 2.44–2.46 (m, 1H), 2.33–2.39 (m, 2H), 2.09–2.11 (m, 1H), 1.74–1.93 (m, 3H), 1.52 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H).

4.3.2.20. (2R,10S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-4-methyl-cyclohexan-1-one 17 [47,53]. Yield 97%, (*anti*/*syn*) = 98:2, enantiomeric excess: 92% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 25 °C, λ = 254 nm; t_R = 63.4 min (*anti*, major), t_R = 46.5 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1H, Ar), 7.53–7.86 (m, 3H, Ar), 5.20 (d, J = 8.4 Hz, 1H), 3.93 (br, 1H), 2.85–2.90 (m, 1H), 2.45–2.47 (m, 1H), 2.35–2.42 (m, 2H), 2.38–2.79 (m, 2H), 1.90–1.93 (m, 1H), 1.64–1.75 (m, 3H), 1.43 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H).

4.3.2.21. (3R,4S)-3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one 18 [47,53]. Yield 90%, (*anti*/*syn*) = 8:92, enantiomeric excess: 95% of *syn*-diastereomer determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 20:80; 0.8 mL/min, 25 °C, λ = 254 nm) t_R = 21.7 min (*syn*, major) and t_R = 16.2 min (*syn*, minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 5.20–5.22 (m, 1H), 4.40–4.42 (m, 1H), 3.71 (d, J = 4.6 Hz, 1H), 2.68 (d, J = 8.1 Hz, 1H), 2.36–2.43 (m, 1H), 2.36 (s, 3H).

4.3.2.22. (3R,4S)-3,4-Dihydroxy-4-(2-nitrophenyl)butan-2-one 19 [47,53]. Yield: 92%, (*anti*/*syn*) = 11:89, enantiomeric excess: 96% of *syn*-diastereomer determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 20:80; 0.8 mL/min, 25 °C, λ = 254 nm) t_R = 14.0 min (*syn*, major) and t_R = 12.9 min (*syn*, minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.11 (dd, J = 8.0, 0.8 Hz, 1H), 7.79–7.81 (d, J = 8.0 Hz, 1H), 7.70–7.74 (t, J = 8.0 Hz, 1H), 7.48–7.53 (t, J = 8.0 Hz, 1H), 5.89 (m, 1H), 4.45–4.56 (m, 1H), 2.51 (s, 3H).

4.3.2.23. (3R,4S)-3,4-Dihydroxy-4-(3-nitrophenyl)butan-2-one 20 [47,53]. Yield: 97%, (*anti*/*syn*) = 18:82, enantiomeric excess: 99% of *syn*-diastereomer determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 15:85; 1.0 mL/min, 25 °C, λ = 254 nm) t_R = 21.0 min (*syn*, major) and t_R = 16.0 min (*syn*, minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (m, 1H, ArH), 8.21 (ddd, J = 8.1, 2.3, 1.1 Hz, 1H), 7.79 (m, 1H), 7.60 (t, J = 7.9 Hz, 1H), 5.21–5.24 (m, 1H), 4.42–4.47 (m, 1H), 3.74–3.75 (m, 1H), 2.72 (d, J = 8.1 Hz, 1H), 2.38 (s, 3H).

4.3.2.24. (S)-4-hydroxy-4-(4-nitrophenyl)butan-2-one 21 [47]. *ee* and *dr* was determined by HPLC analysis (AS-H, Hexane:2-PrOH = 80:20, 0.5 mL/min, 254 nm; t_R (minor) = 21.312min, t_R (major) = 23.777 min).

4.3.2.25. (4S)-4-(2-Chlorophenyl)-4-hydroxybutan-2-one 22 [47,53]. Yield 90% enantiomeric excess: 95% determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, $\lambda = 262$ nm) $t_R = 14.5$ min (*R*-isomer, major) and $t_R = 12.3$ min (S-isomer, minor). ^{1}H NMR (300 MHz, $CDCl_3$):$\delta = 7.64$ (dd, $J = 7.6, 1.6$ Hz, 1H, ArH), 7.19–7.34 (m, 3H, ArH), 5.56 (m, 1H), 3.61 (br., 1H), 2.64–3.03 (m, 2H), 2.22 (s, 3H) ppm.

4.3.2.26. ((4S)-4-(3-Chlorophenyl)-4-hydroxy-4butan-2-one 23 [47,53]. Yield 87% enantiomeric excess: 93% determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, $\lambda = 225$ nm) $t_R = 19.0$ min (*R*-isomer, major) and $t_R = 16.8$ min (S-isomer, minor). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.47$ (s, 1H, ArH), 7.19 (m, 1H, ArH), 7.13 (d, $J = 7.2$ Hz, 1H, ArH), 7.09 (m, 1H, ArH), 5.50 (m, 1H), 3.66 (br, 1H), 2.75, (t, $J = 4.6$ Hz, 2H), 2.21 (s, 3H) ppm.

4.3.2.27. (1R,2S)-1-Hydroxy-2-methyl-1-(4-nitrophenyl)pentan-3-one 24 [47]. *ee* and *dr* was determined by HPLC analysis (OJ-H, Hexane:2-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R (minor) = 16.866min, t_R (major) = 15.780 min).

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2011.12.006.

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